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EXPERIMENTAL STUDY

Investigation of the nephroprotective effect of dexmedetomidine on colistin-induced nephrotoxicity in rats

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ABSTRACT
BACKGROUND: There are very few studies in the literature focusing on whether dexmedetomidine exerts a protective effect on colistin nephrotoxicity. Our study aims to investigate the nephroprotective effect of dexmedetomidine in an experimental model of nephrotoxicity in rats.
METHODS: The control group was administered saline (SF) intraperitoneally twice a day. The colistin group received an intraperitoneal (ip) injection of 10 mg/kg of colistin twice a day. The DX10 group received 10 mg/kg of colistin 20 minutes after the intraperitoneal injection of 10 mcg/kg of dexmedetomidine. The DX20 group received 10 mg/kg of colistin 20 minutes after the intraperitoneal injection of 20 mcg/kg of dexmedetomidine. Applications were continued for 7 days, twice a day. All rats were sacrificed on the 8th day after blood and kidney tissue samples were taken. BUN, Creatine, KIM-1 and Endothelin-1 were studied in blood samples.
RESULTS: There was a significant difference in the median values of Urea, BUN and Creatine between the groups ($p<0.001$, $p<0.001$, $p<0.001$, respectively). There was a significant difference in the median values of KIM-1 and Endothelin-1 between the groups ($p=0.009$, $p=0.001$, respectively). A significant difference was observed between the histopathological scores of the groups ($p<0.001$).
CONCLUSION: Dexmedetomidine significantly decreased the elevated levels of BUN, Creatinine, KIM-1, and Endothelin-1 induced by colistin. Dexmedetomidine, at both doses, histopathologically prevented apoptosis and reduced the number of necrotic cells in the kidneys. Dexmedetomidine provides renoprotective effects, therefore it is a valuable sedation agent for clinicians working in intensive care units *(Tab. 2, Fig. 4, Ref. 19).*
Text in PDF *www.elis.sk*
KEY WORDS: rat, colistin, nephrotoxicity, dexmedetomidine.

Introduction

Intensive Care Unit (ICU) patients consist of patients who undergo invasive procedures frequently, whose hospital stay is longer than other patients due to the general disease condition and who receive broad-spectrum antibiotics frequently. Antibiotic-resistant nosocomial infections, including broad-spectrum carbapenems, are encountered in a significant proportion of ICU cases. The use of colistin, which was avoided in the past years due to its neurotoxic and nephrotoxic effects, has come to the fore again to combat these nosocomial infections (1).

Colistin is one of the major antibiotics used in hospital infections caused by resistant bacteria. The most important and dose-limiting adverse effect of colistin is nephrotoxicity which causes severe morbidity and mortality (2). Nephrotoxicity is related to the duration and the dose of colistin. The mechanism of colistin-induced renal failure is not fully known yet. Proximal tubules are thought to be affected during the process (3).

Dexmedetomidine is a selective α2-adrenoceptor agonist. In addition to their sympatholytic effects, α2-adrenergic agonists also exert analgesic, sedative, anxiolytic and hypnotic effects. Administration of dexmedetomidine infusion inhibits the secretion of renin and antidiuretic hormone (ADH) as a result of the activation of these receptors, stimulating the excretion of water and sodium (Na). Various animal studies have demonstrated the renal protective effect of dexmedetomidine (4, 5).

However, there is a limited number of available studies on whether dexmedetomidine has a protective effect on colistin nephrotoxicity. Our study aims to investigate the nephroprotective effect of dexmedetomidine in an experimental model of nephrotoxicity induced in rats.

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Materials and methods

Our study was designed as a randomized controlled single-blind experimental study. Rats were numbered with labels on their tails and divided into groups. During the study, all experimental and surgical applications were performed per the Guideline for the Care and Use of Experimental Animals published by the U.S. National Institutes of Health considering ethical principles. Ethical consent was obtained from Ordu University Rectorate Local Ethics Committee for Animal Experiments with the number 2020/5 dated 22.07.2020. Following the ethical consent, animal experiments were carried out at Ordu University Experimental Research Center. The subjects were obtained from Samsun Ondokuz Mayis University, Experimental Animal Breeding and Research Center. Financial support was provided by Ordu University Scientific Research Projects Coordination Unit for this project (ODU SRPC-Project number: A-2102).

Forty adult female Sprague-Dawley rats, 10–12 weeks old and weighing 250–300 grams, were used in the study. Rats were kept in the same environment in standard plastic cages and fed with standard rat chow. Tap water was used as drinking water. The environment in which the rats were kept was maintained at room temperature (22 °C). The rats were maintained under a 12/12 hour of light and dark cycle. Experimental animals were divided into four groups, each containing 10 rats. Prior to the experiment, each rat was weighed and the weights were recorded, upon which the appropriate drug dose was calculated.

Group Control (control group, n = 10): The rats in this group were administered an IP injection of 1 ml/kg of saline 20 minutes after an intraperitoneal injection (IP) of 1 ml/kg 0.9 % NaCl solution.

Group COL (colistin group, n = 10): The rats in this group were administered 10 mg/kg of colistin (Colimycin 150 mg im/iv Kocak Farma Ilac) 20 minutes after the administration of 1 ml/kg of saline.

Group DX10 (colistin-dexmedetomidine 10 mcg/kg, n = 10): The rats in this group were administered an intraperitoneal injection of 10 mg/kg colistin (Colimycin 150 mg im/iv Kocak Farma Ilac) 20 minutes after an IP injection of 10 mcg/kg dexmedetomidine (Precedex 200 mcg/2 ml; Hospira, Rocky Mount, NC, USA).

Group DX20 (colistin-dexmedetomidine 20 mcg/kg group, n = 10): The rats in this group were administered an intraperitoneal injection of 10 mg/kg colistin (Colimycin 150 mg im/iv Kocak Farma Ilac) 20 minutes after an intraperitoneal injection of 20 mcg/kg dexmedetomidine (Precedex 200 mcg/2 ml; Hospira, Rocky Mount, NC, USA).

IP injections were administered to each rat from the left lower quadrant with an insulin injector twice a day at 8-hour intervals. Gentle aspiration was performed before each application to avoid intravenous injection. The procedure was continued twice a day for seven days.

All rats were sacrificed on the 8th day before blood and kidney tissue samples were taken. Rats were sedated with 50 mg/kg of Ketamine (Ketalar flk, Pfizer Pharma, GMBH, Germany) and 10 mg/kg of xylazine hydrochloride (Alfazyne 2 % Alfasan, International, Holland) prior to the collection of blood samples. Blood was collected by the intracardiac route with the help of an injector. Both kidneys were exposed by laparotomy, resected and placed in 10 % formalin solution. At the end of the experiment, the rats were sacrificed by cervical dislocation. Collected blood samples were taken into biochemistry tubes. The tubes were centrifuged at 2000 rpm for 15 minutes and the obtained serum was separated into eppendorf tubes and stored at –80 degrees until the experiment day. Urea, BUN (blood urine nitrogen), creatinine (Cre), KIM-1 (Kidney Injury Molecule-1) and Endothelin-1 measurements were performed in serum dissolved at room temperature on the experiment day. Serum urea, BUN, and creatinine levels were measured with colorimetric assay kits while Serum KIM-1 and Endothelin-1 levels were measured with rat ELISA kits.

Sections were excised from renal tissue and 0.5-cm-thick samples were obtained for pathological examination. Collected samples were fixed with 10 % formalin solution. Paraffin blocks were prepared after routine tissue follow-up and two 4–5 μ thick sections were resected from the blocks. The sections were stained with routine hematoxylin-eosin (H&E) and examined under the light microscope according to the classification reported by Houghton et al (6–8). The classification was made as follows:

0: No necrosis or apoptosis, normal cell appearance,

1: Areas of focal granulovacuolar epithelial cell degeneration and granular debris in the tubular lumina with or without evidence of desquamation in small foci (< 1 % of total tubule population involved by desquamation),

2: Tubular epithelial necrosis and desquamation easily seen but involving less than half of the cortical tubules;

3: More than half of the proximal tubules showing desquamation and necrosis, and involved tubules are easily found;

4: Complete or almost complete tubular necrosis.

The sections were evaluated blindly under the light microscope by a single pathologist to determine the amount of apoptosis. The preparations were scanned thoroughly and the percentage of positively stained cells was determined.

Statistical analysis

The data were analyzed with the IBM SPSS v23 software package. Compliance with normal distribution was examined with the Shapiro-Wilk test. One-Way Analysis of Variance was used for the comparison of normally distributed data between three or more groups, and multiple comparisons were analyzed with the Tukey HSD test. Kruskal–Wallis test was used for the comparison of non-normally distributed data between three or more groups and multiple comparisons were analyzed with the Dunn's test. Pearson Chi-Square statistics were used to compare categorical variables between the groups and multiple comparisons were analyzed with the Bonferroni-adjusted Z test. Statistics were presented as mean ± standard deviation and median (minimum-maximum) for quantitative data and as frequency (percentage) for categorical variables. The significance level was considered as $p < 0.05$.

Results

Comparison of Urea, BUN, Cre, KIM-1, and Endothelin-1 values by groups is presented in Table 1.

Tab. 1. Comparison of Urea, BUN, CRE, KIM-1, and Endothelin-1 values by groups.

		Control	COL	DX10	DX20	Test Statistics	p
Urea	Mean±SD	45.62±4.14[a]	55.57±2.8[b]	45.48±5.17[a]	47.36±1.34[a]	17.107	<0.001*
	Median (Min.–Max.)	44.8 (40–55)	55.6 (51.7–59.6)	45.75 (34–52.8)	47.2 (45.8–49.9)		
BUN	Mean±SD	21.35±0.75	24.95±2.04	21.5±2.39	22.55±0.85	17.986	<0.001**
	Median (Min.–Max.)	21.14 (20.51–23.18)[a]	25.1 (21.12–27.78)[b]	22.32 (15.89–23.79)[a]	22.65 (21.4–23.86)[ab]		
Cre	Mean±SD	0.74±0.06	0.86±0.1	0.81±0.07	0.72±0.02	18.733	<0.001**
	Median (Min.–Max.)	0.72 (0.66–0.83)[ac]	0.87 (0.72–1.1)[b]	0.82 (0.71–0.96)[bc]	0.71 (0.7–0.77)[a]		
KIM-1	Mean±SD	0.97±0.12	1.23±0.31	1.16±0.13	1.06±0.12	11.521	0.009**
	Median (Min.–Max.)	0.98 (0.79–1.18)[a]	1.1 (1.03–1.93)[b]	1.2 (0.98–1.34)[b]	1.03 (0.92–1.35)[ab]		
Endothelin-1	Mean±SD	60.2±8.02[a]	73.93±5.23[b]	68.65±9.26[ab]	61.92±6.32[a]	7.372	0.001*
	Median (Min.–Max.)	59.27 (46.8–75.43)	72.09 (66.41–83.85)	68.69 (50.21–82.19)	61.67 (53.06–70.08)		

*One Way Analysis of Variance; **Kruskal Wallis H test; [a–c]There is no difference between groups with the same letter.

Tab. 2. The comparison of histopathological scores between the groups.

Histopathological Score	Control	COL	DX10	DX20	Test Statistics	p*
No Necrosis, n (%) (Score 0)	4 (40)[a]	0 (0)[b]	0 (0)[b]	3 (30)[ab]	36.419	<0.001
Low Necrosis, n (%) (Score 1)	5 (50)[ab]	1 (10)[b]	7 (70)[a]	7 (70)[a]		
Moderate Necrosis, n (%) (Score 2)	1 (10)[a]	2 (20)[a]	3 (30)[a]	0 (0)[a]		
Advanced Necrosis, n (%) (Score 3)	0 (0)[a]	3 (30)[a]	0 (0)[a]	0 (0)[a]		
Complete Necrosis, n (%) (Score 4)	0 (0)[a]	4 (40)[b]	0 (0)[a]	0 (0)[a]		

*Pearson Chi-Square test; [a–b:] There is no difference between groups with the same letter in each line.

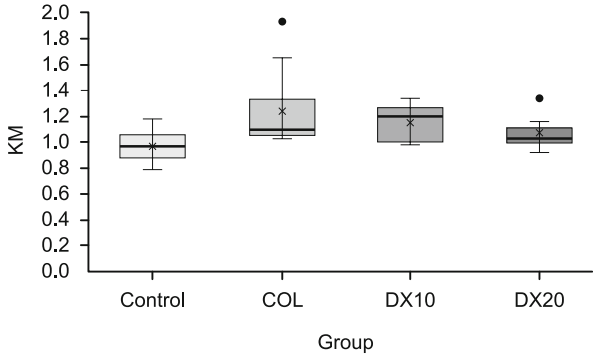

Fig. 1. Box plot graph of KIM-1 values.

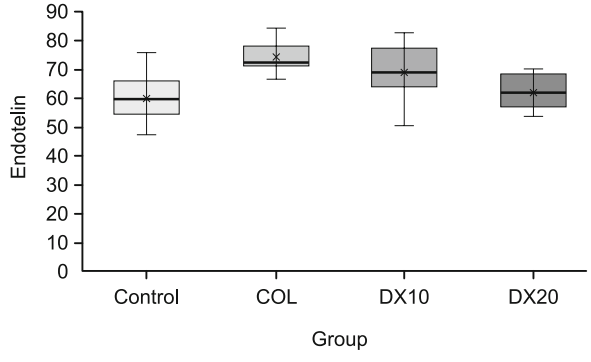

Fig. 2. Box plot graph of Endothelin-1 values.

There was a significant difference in the mean urea values between the groups ($p < 0.001$). The mean value was 45.62 in the control group, 55.57 in the COL group, 45.48 in the DX10 group, and 47.36 in the DX20 group. The difference resulted from the higher median value obtained in the COL group compared to other groups. Urea levels were lowest in the control group and highest in the COL group whereas, lower levels were observed in the DX10 and DX20 groups compared to the COL group and higher levels compared to the control group.

There was a significant difference in the median BUN values between the groups ($p < 0.001$). The median value was 21.14 for the control group, 25.1 for the COL group, 22.32 for the DX10 group, and 22.65 for the DX20 group. The difference resulted from the higher median value obtained in the COL group compared to the median of the control and DX10 groups. BUN levels were the lowest in the control group and the highest in the COL group; whereas lower levels were observed in the DX10 and DX20 groups compared to the COL group and slightly higher levels compared to the control group.

There was a significant difference in the median Creatine values between the groups ($p < 0.001$). The median value was 0.72 for the control group, 0.87 for the COL group, 0.82 for the DX10 group, and 0.71 for the DX20 group. The highest median value was in the COL group, while the lowest median value was in the DX20 group. Creatine levels were the lowest in the control group and highest in the COL group; whereas, lower values were observed in the DX10 and DX20 groups compared to the COL group and slightly higher values compared to the control group.

There was a significant difference in the median KIM-1 values between the groups ($p = 0.009$). The median value was 0.98 for the control group, 1.1 for the COL group, 1.2 for the DX10 group, and 1.03 for the DX20 group. The difference resulted from the difference between the COL and control groups and the control and DX10 groups. The KIM-1 levels were the lowest in the control group and the highest in the COL group; whereas lower levels were observed in the DX10 and DX20 groups compared to the COL group and slightly higher levels compared to the control group.

There was a significant difference in the mean Endothelin-1 values between the groups (p = 0.001). The mean value was 60.2 for the control group, 73.93 for the COL group, 68.65 for the DX10 group and 61.92 for the DX20 group. The difference resulted from the higher mean value obtained in the COL group compared to the means of the control and DX10 groups. Endothelin-1 levels were the lowest in the control group and the highest in the COL group; whereas lower levels were observed in the DX10 and DX20 groups compared to the COL group and slightly higher levels compared to the control group.

Box plot graph of KIM-1 levels is presented in Figure 1.

Box plot graph of Endothelin-1 levels is presented in Figure 2.

The comparison of histopathological scores between the groups is presented in Table 2.

A significant difference was observed between the histopathological scores of the groups (p < 0.001). In the study, 40 % of the subjects in the control group had no necrosis, 40% of the subjects in the COL group had complete necrosis, whereas 70 % of the subjects in the DX10 and DX20 groups had few necrotic cells. The difference resulted from the fact that the absence of necrosis was higher in the control group than the COL and DX10 groups; whereas, the rate of low necrosis was lower in the COL groups than the DX10 and DX20 groups and the rate of complete necrosis was highest in the COL groups compared to all other groups. The rate of necrotic cell density was highest in the control group (40 %) while it was 30 % in the DX20 group. While the rate of low necrosis was lowest in the COL group (10 %), the DX10 and DX20 groups exhibited a rate of 70 %. On the other hand, moderate necrosis was detected as 0 % in the DX 20 group, which suggests that dexmedetomidine has a nephroprotective effect. While the rate of complete necrosis was the highest in the COL group with 30 %, it was determined as 0 % in the control, DX10, DX20 groups. Complete necrosis was the highest in the COL group with 40 %, while it was determined as 0 % in the control, DX10, DX20 groups. This situation, again, strongly suggests that dexmedetomidine has a nephroprotective effect.

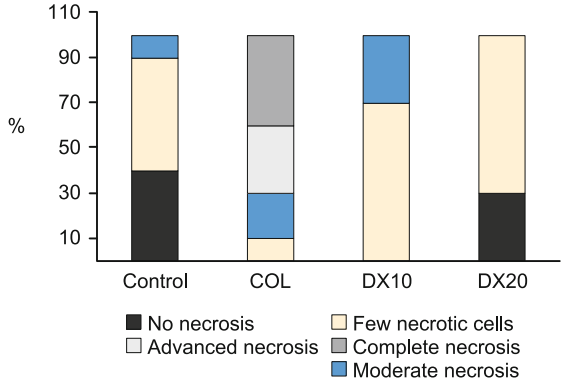

Fig. 3. Clustered column chart of histopathological scores.

Clustered column chart of histopathological scores is presented in Figure 3.

Microscopic view of the scores (Score 0, 1, 2, 3) obtained from the histopathological sections is presented in Figure 4.

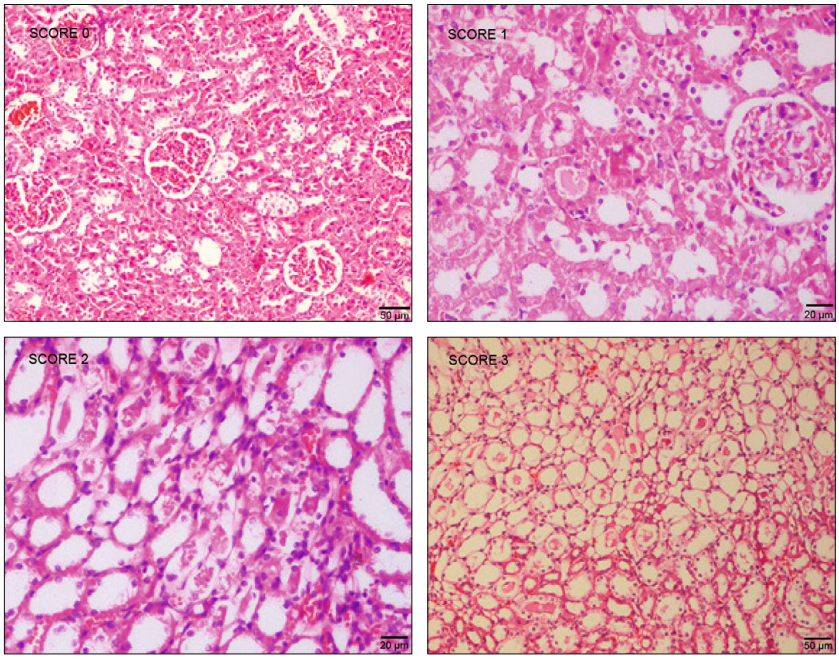

Fig. 4. Histopathological scores obtained from the sections (Score 0, 1, 2, 3).

Discussion

In our experimental study, the biochemical scores exhibit consistency with our H_1 hypothesis. The detection of serum KIM-1 and Endothelin-1 levels at the highest rate in the COL group and the lowest in the control group, as well as the detection of lower values in the DX10 group and the DX20 group than the COL group and slightly higher than the control group, suggest that dexmedetomidine exerts renal protective effects. The fact that KIM-1 and Endothelin-1 levels in the DX20 group are closer to those of the control group supports the idea that "kidney protection increases with higher doses."

Our histopathological findings are also consistent with our H_1 hypothesis. While the necrotic cell density was the lowest in the control group, the highest rate was detected in the COL group. In the DX10 and DX20 groups, advanced necrosis and complete necrosis cell density were not observed, whereas low necrotic cell density was higher in these two groups; which, again, gives us a solid impression that dexmedetomidine plays a nephroprotective effect.

In an experimental study, Sivanesan et al (9) histopathologically demonstrated the protective effect of gelofusine in rats with colistin nephrotoxicity. In the study, the rats were administered 400 mg/kg of gelofusine

intravenously, followed by an injection of colistin 15 minutes after the administration of gelofusine. Histopathological evaluation revealed that gelofusine exerted a renal protective effect, especially preventing damage to the proximal tubules. In our study, we found that dexmedetomidine was protective against nephrotoxicity.

In their study, Ghlissi et al (10) tried to determine nephrotoxicity by administering different doses of colistin in rats. Colistin was administered to rats at doses of 150000, 300000 and 450000 of IU/kg/day for 7 days. Plasma Cystatin-C, Creatine, urine NGAL, GGT, LDH, ALP, AST, ALT values were measured to determine nephrotoxicity. A statistically significant increase was observed in plasma Cystatin-C and urine NGAL values compared to the control group. There was no significant change in other parameters. Researchers reported that Cystatin-C might be a more accurate marker than Creatine and NGAL in colistin nephrotoxicity. In our study, significant results were obtained for both KIM-1 and Endothelin-1 levels, therefore it can be recommended to monitor KIM -1 and Endothelin-1 levels in the clinical follow-up of nephrotoxicity.

A clinical study conducted by Sirijatuphat et al (11) investigated whether ascorbic acid plays a protective role in colistin-related nephrotoxicity. Fifteen patients were administered colistin only while 15 patients were administered ascorbic acid combined with colistin. The authors compared urinary NGAL excretion and N-acetyl glucosaminidase excretion, reporting no statistical difference between the two groups and they concluded that ascorbic acid is not a good choice in colistin nephrotoxicity. In our study, it was determined that dexmedetomidine exerts a nephroprotective effect. Dexmedetomidine is an agent used for sedation in intensive care patients, while polymyxins (colistin and polymyxin-B) are among the antibiotics frequently preferred in ICU patients for resistant infections. Therefore, we can say that dexmedetomidine can be used as an effective sedative agent for ICU patients.

Plasma BUN and Creatine were measured in the study conducted by Ozyilmaz et al (12) investigating the effect of N-acetyl cysteine (NAC) on colistin nephrotoxicity in rats. The rats were divided into three groups and drug administration was continued for 6 days. BUN and creatin levels were significantly elevated in the colistin group (300000 IU/kg) compared to the control group; however, no significant change was observed in the values of the NAC-treated group. In the same study, BUN, plasma TNF-α, renal tissue superoxide dismutase (SOD), and malondialdehyde (MDA) levels were measured alongside Creatine. It was shown that SOD, i-NOS, NT-3 values increased in the colistin group and decreased in the NAC group. Accordingly, it was reported that colistin-induced renal damage may result from oxidative stress and that NAC treatment can reduce the damage with its antioxidant effects. Similarly, we investigated the BUN and Creatine values in our study. Ozyilmaz et al (12) found that NAC provided reno-protective effects. Similarly, the reno-protective effect of dexmedetomidine was demonstrated in our study.

In the literature, different studies investigated the protective effect of dexmedetomidine on organs. Bayram et al (13) applied intraoperative dexmedetomidine infusion to patients who underwent percutaneous nephrolithotomy and evaluated renal functions. The study failed to reveal a positive effect of dexmedetomidine on NGAL, Cystatin-C and Creatin clearance, but it was reported to reduce renin levels significantly. Another study by the same researchers investigated the effect of dexmedetomidine on renal functions in contrast to material-induced nephropathy in pediatric patients undergoing cardiac angiography. It was reported that dexmedetomidine inhibited the elevation of plasma Endothelin-1 and renin, thus may reduce renal damage (14).

The study of Kocoglu et al (15), in which the effect of dexmedetomidine on histological changes was investigated in rats induced with renal ischemia-reperfusion injury, reported that dexmedetomidine reduced the renal damage resulting from ischemia-reperfusion injury. Although it has not been investigated how dexmedetomidine exerts such an effect, it has been reported that it might be associated with the sympathetic discharge suppressing the secretion of presynaptic norepinephrine, thereby increasing renal blood flow and glomerular filtration rate. In addition, Si et al (16) conducted an experimental study reporting that dexmedetomidine inhibited long-term inflammation due to renal ischemia-reperfusion injury. Our study results are in full agreement with the literature findings.

Liang et al (17) investigated the effect of dexmedetomidine on acute kidney injury that developed after the administration of cisplatin in rats, where they administered 25 μcg/kg of dexmedetomidine once a day after cisplatin administration. The results of Bax, p53, caspase3 activity, and histological evaluation showed that dexmedetomidine provides renal protection by regulation of apoptosis and inflammatory response in cisplatin-induced acute kidney injury. Our results are also consistent with the literature findings.

A retrospective study by Kwiatkowski et al (18) conducted in a pediatric intensive care unit investigated whether dexmedetomidine exerted a protective effect against postoperative acute kidney injury developed in pediatric patients undergoing cardiopulmonary bypass. The study results showed that the incidence of acute kidney injury was lower in patients receiving dexmedetomidine. In the study, it was emphasized that the working mechanism of dexmedetomidine was not fully understood; however, it was reported that the combination of its anti-inflammatory, cytoprotective and sympatholytic effects might have been effective. Available clinical studies have demonstrated the reno-protective effects of dexmedetomidine.

Other factors facilitating the development of nephrotoxicity in intensive care units, that is, facilitating the development of acute kidney injury, should be well observed by the clinician. Renal functions should be monitored more carefully in ICU patients, especially if they are administered polymyxin-group antibiotics or other agents accused of nephrotoxicity, such as vancomycin. Clinical conditions associated with kidneys, such as hypotension, major surgery, stroke, myocardial infarction, pulmonary embolism, and septic shock should be further investigated in ICU patients. The use of vasoactive medications, mechanical ventilation, lactate levels, which are severe disease indicators, should be monitored and the clinician should be aware of patient comorbidities, especially chronic kidney disease (19). The results of our study show that the nephroprotective effect of dexmedetomidine can be useful in the fight against nephrotoxicity in ICU patients, as well as in cases where sedation is required.

In conclusion, we determined that dexmedetomidine exerted a protective effect in colistin-related nephrotoxicity by means of histopathological and biochemical markers. Dexmedetomidine causes a significant reduction in the elevation of BUN, Creatinine, KIM-1 and Endothelin-1 values induced by colistin. Dexmedetomidine histopathologically inhibited apoptosis in the kidneys at both doses and decreased the number of necrotic cells. Dexmedetomidine exerts reno-protective effects, therefore it is a very valuable sedation agent for clinicians in intensive care units. We believe that our experimental study will shed light on prospective clinical studies.

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