The Effects of Cerium Oxide on Sevoflurane Anesthesia and its Relationship to Renal Injury in Rats

Seryum Oksidin Sevofluran Anestezisi Üzerine Etkileri ve Böbrek Hasarı ile İlişkisi

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ABSTRACT

Objective: The goal of this research was to determine whether cerium oxide could protect against kidney tissue damage in rats given sevoflurane anesthesia.
Material and Methods: After the approval of the Ethics Committee, study was conducted in Gazi University Animal Research Laboratory, Ankara, Turkey, in April 2019. 24 rats were divided into 4 groups: control group (C), cerium oxide group (CO), sevoflurane group (S), and cerium oxide-sevoflurane group (COS). 0.5 mg/kg doses of intraperitoneal cerium oxide was administered to the CO and COS groups 30 minutes before the procedure. Sevoflurane (2.3%) was administered to the S and COS groups for 3 hours. Histopathological and biochemical parameters were then analyzed.
Results: Malondialdehyde (MDA) level and superoxide dismutase (SOD) activity were significantly higher in group S than in group C and CO. On the other hand, MDA level and SOD activity were significantly lower in group COS than in group S. Tubular dilatations markedly increased in group S and COS compared to group C (p=0.002, p=0.009, respectively). Tubular dilatation was also significantly higher in group S than in group CO. Tubular cell necrosis were significantly higher in all groups than in group C. Tubular cell necrosis was also significantly higher in group S compared to group CO. Bowman's space dilatations were significantly higher in groups S and COS compared to the C group. Bowman's space dilatation was also significantly higher in group S than in group CO. Tubular cell shedding was significantly higher in group S compared to group C and CO. Tubular cell necrosis and cell shedding were found to be significantly lower in group COS than in group S.
Conclusion: We conclude that pretreatment of rats with a single intraperitoneal dose of cerium oxide nanoparticles is safe to prevent kidney damage caused by sevoflurane anesthesia in rats.

Keywords: Cerium oxide, sevoflurane, kidney, rat

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ÖZET

Amaç: Bu araştırmanın amacı, sevofluran anestezisi verilen sıçanlarda seryum oksidin böbrek dokusu hasarına karşı koruyucu olup olmadığını belirlemekti.
Yöntem: Çalışma Etik Kurul onayı alındıktan sonra Nisan 2019'da Gazi Üniversitesi Hayvan Araştırma Laboratuvarı Ankara'da gerçekleştirildi. 24 rat kontrol grubu (K), seryum oksit grubu (SO), sevofluran grubu (S) ve seryum oksit-sevofluran grubu (SOS) olmak üzere 4 gruba ayrıldı. SO ve SOS gruplarına işlemden 30 dakika önce 0.5 mg/kg intraperitoneal seryum oksit verildi. S ve SOS gruplarına 3 saat sevofluran (%2.3) verildi. Daha sonra histopatolojik ve biyokimyasal parametreler analiz edildi.
Bulgular: Malondialdehit (MDA) düzeyi ve süperoksit dismutaz (SOD) aktivitesi grup S'de grup K ve SO'ya göre anlamlı olarak yüksek bulundu. Öte yandan, MDA düzeyi ve SOD aktivitesi SOS grubunda grup S'ye göre anlamlı derecede düşüktü. Tübüler dilatasyon grup K'ye göre grup S ve SOS'ta belirgin olarak arttı (sırasıyla p=0.002, p=0.009). Grup S'de tübüler dilatasyon da Grup SO'ya göre anlamlı olarak yüksekti. Tübüler hücre nekrozu tüm gruplarda Grup K'ye göre anlamlı olarak yüksekti. Tübüler hücre nekrozu da grup SO'ya kıyasla grup S'de anlamlı derecede yüksekti. Bowman'ın boşluk dilatasyonu da grup S'de grup SO'dan önemli ölçüde daha yüksekti. Grup S'de tübüler hücre dökülmesi grup K ve SO'ya göre anlamlı derecede yüksekti. Tübüler hücre nekrozu ve hücre dökülmesi grup SOS'da grup S'ye göre anlamlı derecede daha düşük bulundu
Sonuç: Sıçanlarda sevofluran anestezisinin neden olduğu böbrek hasarını önlemek için sıçanlara intraperitoneal tek doz seryum oksit nanopartikülleri ile ön tedavinin güvenli olduğu sonucuna vardık.

Anahtar Sözcükler: Seryum oksit, sevofluran, böbrek, sıçan

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INTRODUCTION

In recent years, scientists have succeeded in producing nanoparticles of various sizes and morphologies. Cerium oxide, the most reactive compound stemming from the Lanthanide series, is a rare-earth oxide material and is among these nanoparticles. These nanoparticles have been used in industrial fields, such as in polishing, conversion of toxic gases, and they are found in sensors and catalysts (1). Cerium oxide nanoparticles (CNPs) have been shown in several studies to exhibit radiation protection (2), anti-inflammatory properties (3), neuroprotective benefits (4), and anti-ischemic stroke protection (5). In addition to these properties, since the antioxidant potential has been discovered on nanoparticle surfaces, CNPs have gained great importance in medical research for the treatment of various oxidative stress related disorders (5).

Because of its pharmacologic and pharmacokinetic characteristics, as well as the lack of severe adverse effects on multiple organ systems, sevoflurane has been regarded as a reliable volatile anesthetic agent for clinical applications in all over the world (6). However, in recent years, due to their toxicity and potential side effects, the safety of volatile anesthetics has become controversial (7). Several investigations have demonstrated that inorganic fluoride, which is generated by the biotransformation of sevoflurane with hepatic cytochrome enzymes, can be harmful to liver and kidney tissues in both humans and animals. (8-10). Numerous research have investigated the nephrotoxic potential of sevoflurane in humans (11-13) and various laboratory animal species (14), however there is no study investigating the effect of sevoflurane anesthesia on kidney damage. The goal of this study is to explain whether CNPs can protect rats from sevoflurane induced kidney damage.

MATERIALS and METHODS

Animals

This study was approved by the Gazi University Experimental Animals Ethics Committee (Ethics number: G.U.ET-18-052) and conducted in April 2019 in accordance with the Laboratory Animal Care and Use Guide in the Experimental Animals Laboratory in Ankara/Turkiye.

Experimental Design

In this research, 24 male Wistar albino rats weighing 250–330 grams were used. Rats were kept in separate cages under a constant temperature (22 °C ± 2 °C) and standard conditions with a 12-hour light/dark cycle and free access to food pellets and tap water. The procedures were carried out in four groups, each with six rats assigned randomly. The groups included control group (group C), cerium oxide group (group CO), sevoflurane group (group S), and cerium oxide-sevoflurane group (group COS). 0.5 mg/kg doses of cerium oxide (15) was given 30 minutes prior to anesthesia, then sevoflurane (2.3%) was administered for 3 hours to the S and COS groups. Renal tissue samples were taken at the end of the experimental period. The renal tissue specimens were removed then stored at −80 °C.

Biochemical Determinations

The kidney tissues washed with cold NaCl solution (0.154 M) then homogenized in a Diax 900; Heidolph Instruments GmbH&Co KG, Schwabach, Germany at 1000 U for about 3 min. After centrifugation the upper clear layer was taken.

Van Ye et al method (16) was used for measuring the MDA levels and thiobarbituric acid (TBA) reactive substances. Since MDA or similar substances react with TBA to produce a pink pigment with a maximum absorption of 532 nm, the reaction with TBA at 80-90 ˚C is used to determine the MDA level. The sample is mixed with cold 20% (w/v) trichloroacetic acid to induce protein precipitation. The precipitation is then centrifuged at 3000 rpm for 10 minutes at room temperature to form a pellet. An aliquot of the supernatant is placed in an equal volume of 0.6% (wt/vol) TBA in a boiling water bath for 30 minutes. Sample and blank absorbance were read at 532 nm and the results were expressed as nmol/mg protein. Paraoxonase 1 (PON-1) activity was measured according to Brites FD method (17). Paraoxon hydrolysis rate was measured by monitoring the increase in absorbance at 405 nm at 25 °C.

Superoxide dismutase (SOD) activity was determined according to the method of Durak I et al. (18). The basis of this method is the reduction of nitro blue tetrazolium (NBT) in the reaction medium when the superoxide radical is formed by the xanthine-xanthine oxidase system. Absorbance was measured spectrophotometrically at 560 nm and SOD activity in kidney tissues was expressed as U/mg protein.

The nitric oxide (NO) level was determined using the method developed by Durak et al. (19). The NO pool (mainly consisting of NO•+NO2−) measurement is based on the same chemical reaction, inwhich to a greater extent nitric oxide (NO) and to a lesser extentnitrite anion (NO2−), but not nitrate anion (NO3−), react with sulphanilic acid to produce diazotization. The absorbance of complex-one formed with N-(1-napthyl-ethylene diamine) reflects the sum of NO• and NO2− levels in the reaction medium, which is termed the NO pool in the present study. In this method, sodium nitroprusside is used as the chemical standard. A linear regression was conducted using the peak areas from the standards. The resulting equation was then used to calculate the unknown sample concentrations; the results are expressed as µmol/mg protein.

Histological Determination

During the dissections of the experimental animals, each kidney tissue was taken in sufficient size for histological examinations and was kept in a 10% buffered formaldehyde solution for 24–48 hours for fixation. After fixation, 5-µm-thick sections were taken from tissue samples embedded in paraffin using a routine histological follow-up method with the help of a microtome. The sections were stained using the hematoxylin-eosin (HE) (Bio-optica, Milano, Italy) staining method and then examined under a microscope and photographed.

Statistical Analysis

SPSS version 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The differences between groups were assessed using the Kruskal-Wallis test with a post-hoc Bonferroni-adjusted Mann-Whitney U test. Results were expressed as mean ± standard deviation (SD). The level of significance was set at $p<0.05$

RESULTS

Biochemical Results

Notable differences between groups were discovered in MDA levels in kidney tissue ($p = 0.013$). The MDA level in group S was significantly higher than those in groups C and CO ($p = 0.014$, $p = 0.045$, respectively). MDA level was significantly lower in group COS than that measured in group S ($p = 0.004$). NO level was significantly different between the groups in kidney tissue ($p = 0.022$). NO level was significantly lower in group S than in group C and CO ($p = 0.021$, $p = 0.022$, respectively). In group COS, the NO level was significantly higher than that measured in group S ($p = 0.004$). Similarly, kidney tissue SOD activity between the groups was significantly different ($p = 0.022$). In group S, SOD activity was significantly lower than that measured in group C and CO ($p = 0.005$, $p = 0.018$, respectively). In group COS, SOD activity was significantly higher than that measured in group S ($p = 0.044$; Table 1).

Table 1. Biochemical data of renal tissue (mean ± SD).

	Group C (n = 6)	Group CO (n = 6)	Group S (n = 6)	Group COS (n = 6)	P^{**}
Malondialdehyde (nmol/mL)	0.63 ± 0.03	0.68 ± 0.07	0.84 ± 0.08$^{*\&}$	0.55 ± 0.03^{+}	0.013
Nitric oxide (µmol/L)	69.71 ± 1.61	69.66 ± 1.77	61.42 ± 2.58$^{*\&}$	72.12 ± 3.08^{+}	0.022
Paraoxonase 1 (ng/mL)	46.21 ± 1.58	45.28 ± 1.89	42.92 ± 2.18	41.59 ± 2.02	0.334
Superoxide dismutase (ng/mL)	2.51 ± 0.13	2.44 ± 0.05	2.11 ± 0.09$^{*\&}$	2.33 ± 0.08^{+}	0.028

P^{**}: Significance level $p < 0.05$ by Kruskal-Wallis test
* $p < 0.05$ compared to group C
$^{\&}$ $p < 0.05$ compared to group CO
$^{+}$ $p < 0.05$ compared to Group S

Histopathological Results

In terms of tubular dilatation, Bowman's space dilatation, and tubular cell shedding, there were significant different between the groups (p = 0.008, p = 0.001, p = 0.003; respectively). Tubular dilatation was markedly higher in group S and COS compared to group C (p = 0.002, p = 0.009, respectively). Additionally, tubular dilatation was considerably higher in group S compared to group CO (p = 0.042). Tubular cell necrosis was noticeably higher in all groups than in group C (p < 0.0001 for all).

Tubular cell necrosis was also significantly higher in group S compared to group CO (p < 0.0001). Bowman's space dilatations were significantly higher in group S and COS compared to group C (p < 0.0001, p = 0.005, respectively). Bowman's space dilatation was also significantly higher in group S than in group CO (p = 0.005). Tubular cell shedding was significantly higher in the S group compared to the C and CO groups (p = 0.001, p = 0.001, respectively). In the COS group, tubular cell necrosis and cell shedding were significantly lower than those measured in group S (p = 0.006, p = 0.007, respectively; table 2, figures 1–3).

Table 2. Histopathological data of renal tissue (mean ± SD).

	Group C (n = 6)	Group CO (n = 6)	Group S (n = 6)	Group COS (n = 6)	P^{**}
Tubular dilatation	0.17 ± 0.17	0.50 ± 0.22	1.00 ± 0.00$^{*\&}$	0.83 ± 0.17*	0.008
Tubular cell necrosis	0.17 ± 0.17	1.33 ± 0.22*	2.67 ± 0.21$^{*\&}$	1.83 ± 0.17^{*+}	< 0.0001
Bowman's space dilatation	0.00 ± 0.00	0.33 ± 0.21	1.00 ± 0.00$^{*\&}$	0.67 ± 0.21*	0.001
Lymphocytic infiltration	0.00 ± 0.00	0.33 ± 0.21	0.67 ± 0.21	0.17 ± 0.17	0.068
Tubular cell shedding	0.17 ± 0.17	0.17 ± 0.17	1.00 ± 0.00$^{*\&}$	0.33 ± 0.21^{+}	0.003

P^{**}:

Significance level p < 0.05 by Kruskal-Wallis test, * $p < 0.05$ compared to Group C, $^{\&}$ $p < 0.05$ compared to group CO, $^{+}$ $p < 0.05$ compared to Group S

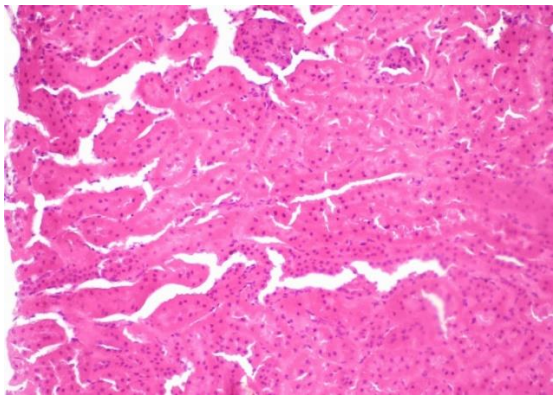

Figure 1. Group C: the control group with normal kidney tissue (hematoxylin & eosin x200).

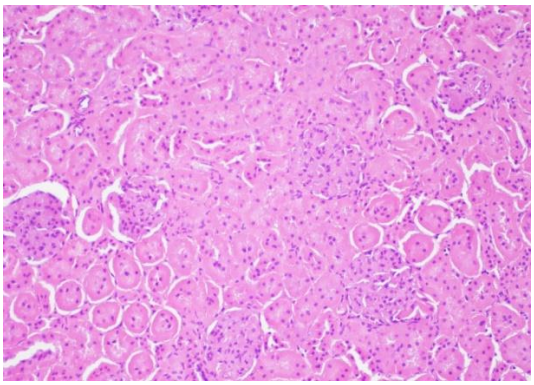

Figure 2. Group S: the sevoflurane group kidney tissue.
Common atrophy, loss of the brushy edge, presence of a pycnotic nucleus and eosinophilic cytoplasm were observed in the tubules (hematoxylin & eosin x200).

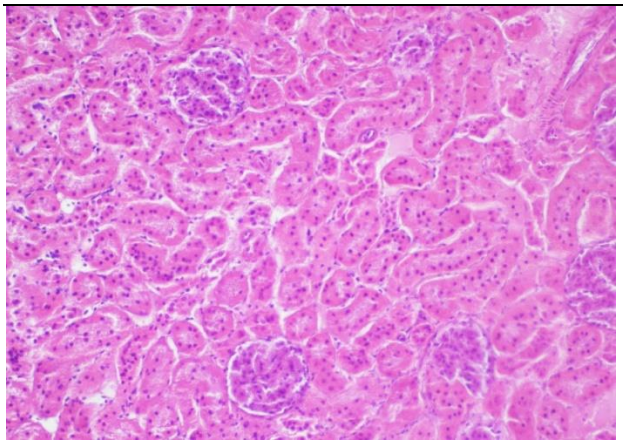

Figure 3. Group COS: the cerium oxide-sevoflurane group kidney tissue. In cross-sections, tubule damage is lighter, the details of the tubule epithelium and glomerular epithelial cells are partially selected. Atrophy and associated loss of the brushy edges are observed in part of the tubule epithelium (hematoxylin & eosin x200).

DISCUSSION

Two main findings of this study is important. First, tubular necrotic damages were observed, especially in the renal tubule epithelium of rats, as well as an increased lipid peroxidation and decreased antioxidant capacity induced by sevoflurane. Second, 0.5 mg/kg cerium oxide nanoparticles used before a sevoflurane application as a pretreatment reduced the oxidant damage on the renal tubular area. According to the oxidant/antioxidant parameters, the increase in lipid peroxidation and decrease in antioxidant capacity suggests that reactive oxygen radicals may play a role in the damage mechanisms caused by sevoflurane on the renal tubules.

Because of its low solubility, sevoflurane is washed in and out from the blood rapidly. Compared to other volatile agents, sevoflurane provides a faster inhalational induction, along with a rapid and smooth recovery. That is why it has been the most preferred inhaled agent over the last 20 years. However, compound A and inorganic fluoride, degradation products of sevoflurane, cause renal injury (20, 21). However, the main mechanism that determines the severity of renal injury in rats is the duration of exposure to compound A and its concentration. According to Gonsowski and colleagues, with minimal histopathological changes, the nephrotoxicity threshold seems to be three hours of sevoflurane exposure (22). Keller et al. argued that sevoflurane is nephrotoxic in rats and they described the renal changes, as tubule cell swelling and/or necrosis in the corticomedullary junction histopathologically (9). Similar to these results, we found tubular dilatation, tubular cell necrosis, and cellular shedding in rats after three hours of sevoflurane administration.

Oxygen is a necessary molecule for aerobic organisms to survive. During mitochondrial oxygen consumption for energy production, reactive oxygen species (ROS) are constantly released. Oxidative stress is caused by an imbalance between ROS production and its scavenging system (23). A major contributor to tissue damage, oxidative stress has been associated with a number of diseases. The kidney is the most susceptible organ to hypoxia, and the renal hypoxia is common on kidney disease progresses. As shown below, hypoxia must play an important role in the progression of oxidative stress in kidney disease (24).

Lipid peroxidation is one of the most sensitive indicators on cellular oxidative response. MDA is formed as an end product of lipid peroxidation and generated by the decomposition of polyunsaturated fatty acids (16). Uremic patients has a high MDA serum concentration.elevated plasma MDA levelmay be an early prognostic indicator of graft dysfunction after a kidney transplantation (25). Studies using sevoflurane have shown MDA levels might vary widely. Allaouchiche et al. investigated the effects of propofol, sevoflurane, and desflurane on oxidative stress and showed that sevoflurane does not cause oxidative damage. In a clinical study by Sivaci et al., examined the effects of sevoflurane on oxygen radicals in patients undergoing a laparoscopy. The authors reported an important increase in the MDA levels in patients receiving sevoflurane compared to the control participants (26). In our current study we observed that the application of sevoflurane for 3 hours significantly increased the MDA levels in rat kidney tissue in comparison with control values.

Multiple antioxidant systems try to protect kidney tissues and cells from oxidative stress caused by ROS. The first intrinsic enzymes that combat oxidative stress are the SOD isoforms. SOD catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide (27, 28). In our current study, SOD enzyme activity was significantly decreased in sevoflurane-treated rats. Ultimately, considering the mechanism of renal damage due to sevoflurane, we think that not only compound A and inorganic fluoride mechanisms, but also the deterioration of the oxidant/antioxidant balance by renal hypoxia due to decreasing of renal blood flow, should be considered.

NO is an antioxidant molecule synthesized in the rats proximal tubules. It has a function as one of the mediators in rat tubular hypoxia and reoxygenation injury. Reduced NO levels are linked to impaired vasorelaxation of renal resistance arteries and diapedesis of polymorphonuclear leukocytes and monocytes (29, 30). Our study showed that decreasing serum NO levels, caused damage, especially at the tubular level, due to sevoflurane compared to the control group. Increased NO levels with the application of cerium oxide 30 minutes before the sevoflurane inhalation suggests that, we can prevent damage due to sevoflurane, especially at the tubular level.

Paraoxonase, a high-density lipoprotein associated with esterase, protects lipoproteins from oxidation. Lipid oxidation could have a key role in the progression of micro and macrovascular disorders., In clinical and animal studies, it has been shown that paraoxonase activity is decreased in atherosclerosis, diabetes, and myocardial infarction (31-33). In addition, in patients suffering from chronic renal failure (CRF), especially when dialysis is required, PON activity has been shown to decrease (34). In our study, PON activities were similar in all groups. PON has antioxidant activities on vulnerable vascular walls and cellular stress. We believe that sevoflurane does not cause renal damage with vascular stress or an atherosclerotic background.

In many in vitro and animal studies many therapeutic antioxidant substances, such as N-acetyl cysteine (NAC), edaravone, and vitamin E, have been chosen for treatment of renal failure caused by oxidative damage (35-37). However, it should not be overlooked that when the same antioxidant molecules are tested in humans, these effects may be below what is expected in terms of their potential, or even worsen the current kidney failure (28). The purpose of this study was to evaluate the antioxidant properties of cerium oxide nanoparticles, whose popularity has increased in the last decade parallel with nanotechnological developments in the field of medicine. Manne et al. investigated the effects of cerium oxide on sepsis-induced renal injury. They suggested that cerium oxide nanoparticles provide protection against acute kidney injury due to severe polymicrobial damage when administered in a single, *stand-alone* dose. Their data suggests that the CNP acts by scavenging ROS, which are linked to reduced caspase-3 activation, reduce the loss of F-actin, and attenuate the tubules injury (15). Our results showed that pretreatment with a 0.5 mg/kg single intraperitoneal dose of CNP has protective effects against sevoflurane-induced kidney damage. Improvements in kidney structure, especially in tubular areas, were accompanied with the attenuation of the oxidant/antioxidant status.

Several recent publications have indicated that exposure to CNPs can cause adverse effects to human health by generating ROS, leading to oxidative stress and inflammation, which causes stress-induced programmed cell death (apoptosis). However, the majority of studies addressing CNP-related toxicity have only used in vitro models or in vivo intratracheal instillation methods (38-40). For these reasons, we designed this study in rats, and we preferred single-alone low doses of intraperitoneal cerium oxide. According to our results, 0.5 mg/kg cerium oxide nanoparticles did not induce the process of lipid peroxidation in any tested period, and also not induce any antioxidant decreases in activity in analyzed enzymes in rats.

CONCLUSION

The safety and antioxidant potential of CNPs were investigated in this study by assessing numerous oxidative stress markers and histopathological evaluations of renal tissue Based on our findings, we can say that a single dose of CNP pretreatment under sevoflurane anesthesia is safe in terms of kidney damage.

It could be concluded that the use of CNPs in the medical field appears to be safe and confers protective behaviors against oxidative stress nevertheless further experimental and clinical researchs are needed to demonstrate the efficacy and safety of various, or repetitive, nanoparticles doses.

Conflict of interest
No conflict of interest was declared by the authors.

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