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The effect of cerium oxide on liver in sevoflurane-administered rats: an experimental study

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Abstract

Background Sevoflurane, a commonly used inhalational anesthetic, has been associated with hepatotoxicity, although reports are often isolated. Cerium oxide nanoparticles (CeO_2) are effective free radical scavengers with potential therapeutic applications for oxidative stress-related damage. This study aimed to evaluate the protective effects of CeO_2 on liver damage in sevoflurane-administered rats.

Methods A total of 24 male Wistar albino rats were randomized into four groups: Control (C), Sevoflurane (S), Cerium Oxide (CeO_2), and Sevoflurane + Cerium Oxide (S + CeO_2). Sevoflurane was administered at 2% concentration with 100% oxygen at 4 L/min for 2 h in Groups S and S + CeO_2. CeO_2 (0.5 mg/kg) was administered intravenously in Groups CeO_2 and S + CeO_2. Biochemical analyses of alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), hemoglobin (Hgb), and hematocrit (Hct) were performed, and liver tissues were examined histopathologically.

Results Hydropic degeneration and neutrophil infiltration were significantly lower in Group CeO_2 compared to Group S. Group S showed elevated AST and LDH levels compared to the control ($p < 0.05$). Although AST levels were lower in Groups CeO_2 and S + CeO_2 than in Group S, the difference was not statistically significant. LDH levels were significantly lower in Group S + CeO_2 compared to Group S ($p = 0.045$). Histopathological examination confirmed reduced liver damage in CeO_2-treated groups.

Conclusions This study is of significance since it is the first experimental study on the effect of CeO2 on liver damage caused by sevoflurane. Cerium oxide demonstrated potential in mitigating sevoflurane-induced liver damage. Further research is warranted to explore the clinical relevance of CeO_2 in hepatic injury.

Keywords Cerium oxide, Sevoflurane, Liver damage, Oxidative stress, Nanoparticles

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Introduction

Nanotechnology continues to revolutionize various scientific fields, particularly in medicine and biomedical research [1]. The ability to manipulate materials at the nanoscale has led to the development of innovative solutions for drug delivery, imaging, and regenerative medicine [2]. Among nanomaterials, cerium oxide nanoparticles (CeO_2) have gained significant attention due to their remarkable redox properties and potential antioxidant effects [3]. Their unique capacity to alternate between Ce^{3+} and Ce^{4+} oxidation states enables continuous scavenging of reactive oxygen species (ROS) [4], making them promising candidates for applications in biomedicine, particularly in conditions related to oxidative stress and inflammation [5].

CeO_2 have demonstrated therapeutic potential in a variety of diseases, including neurodegenerative disorders, cardiovascular diseases, and cancer [6]. Their antioxidant properties have been leveraged to mitigate cellular damage in models of ischemia-reperfusion injury [7], radiation-induced toxicity [8], and inflammatory diseases [9]. Despite these promising effects, research on their hepatoprotective properties remains limited. Given the critical role of oxidative stress in liver diseases, investigating the impact of CeO_2 on hepatic tissue damage is essential for exploring new therapeutic strategies.

Sevoflurane, a widely used volatile anesthetic, has been associated with oxidative stress and hepatotoxic effects in experimental and clinical settings. Although severe hepatotoxicity due to sevoflurane is rare and mostly reported as isolated cases, its increasing use in anesthesia raises concerns about potential liver damage. Approximately 5% of a sevoflurane dose undergoes biotransformation [10], leading to the production of reactive metabolites such as Compound A, which may contribute to hepatotoxicity [11]. Moreover, sevoflurane has been shown to increase cytosolic free calcium (Ca^{2+}) levels and generate oxidative stress, leading to hepatocyte necrosis, particularly with repeated exposure [12, 13]. However, the exact mechanisms underlying sevoflurane-induced liver injury remain unclear.

Given the strong antioxidant properties of CeO_2, their potential protective effects against sevoflurane-induced liver damage warrant investigation. This study aims to evaluate the hepatoprotective role of CeO_2 in sevoflurane-administered rats by examining biochemical and histopathological changes in liver tissue. Furthermore, the study will explore the anti-inflammatory and oxidative stress-modulating mechanisms of CeO_2, contributing to a deeper understanding of their biomedical applications.

By assessing the therapeutic potential of CeO_2 in this experimental model, our research provides new insights into their applications in anesthesiology and hepatology. These findings may pave the way for future studies investigating CeO_2 as novel therapeutic agents for preventing anesthesia-induced hepatic injury and other liver-related disorders.

Methods

Study design and setting

This experimental study was performed at the Gazi University Experimental Animals Research Center, Ankara, Turkey, in August 2019. Ethical approval was obtained from the Gazi University Experimental Animals Ethics Committee (Approval Code: G.Ü.ET-12.042, dated 08.07.2019).

Animal model

In the present study, a total of 24 female Wistar albino rats (age, 5 months; weight, 250-350 g), which were supplied by Gazi University Experimental Animals Research Center, were used. Animals were housed in steel cages under controlled environmental conditions (12-hour light/dark cycles, 20–21 °C temperature, %45–55 humidity) with access to food and water ad libitum. All the experimental procedures were performed according to the Guide for the Care and Use of Laboratory Animals.

The rats were randomly divided into four groups ($n = 6$ per group): Control, Sevoflurane, Cerium Oxide, Sevoflurane + Cerium Oxide groups.

1. **Control Group (C)**: The control groups were not subjected to any intervention. Rats were anesthetized.
2. **Sevoflurane Group (S)**: The rats were exposed to 2% sevoflurane (Sevorane, Abbott, 250 mL) in 100% oxygen at a flow rate of 4 L/min for 2 h, as described in the study by Arslan et al. [14]. Subsequently, the rats were anesthetized.
3. **Cerium Oxide Group (CeO_2)**: A dose of 0.5 mg/kg CeO_2 (CeO_2 aqueous nanoparticle dispersion, 100 mL; Sigma-Aldrich; Merck KGaA) was administered intravenously through the tail vein, as described in the study by Manne et al. [15]. After 150 min, the rats were anesthetized.
4. **Sevoflurane + Cerium Oxide Group (S + CeO_2)**: A dose of 0.5 mg/kg CeO_2 was administered intravenously 30 min prior to sevoflurane exposure. The rats were then exposed to 2% sevoflurane (Sevorane, Abbott, 250 mL) in 100% oxygen at a flow rate of 4 L/min for 2 h. Subsequently, the rats were anesthetized.

Anesthesia and tissue collection

All rats were anesthetized using intramuscular ketamine hydrochloride (50 mg/kg; Ketalar; Parke-Davis Eczacibasi; Pfizer, Inc.) and xylazine hydrochloride 2% (10 mg/

kg; Alfazyne; Ege Vet). The procedure was conducted under a heating lamp with the rats positioned in the supine position. After aseptic preparation of the skin, a midline abdominal incision was performed, exposing the abdominal aorta. All the rats were sacrificed by collecting blood (5-10 ml) from their abdominal aorta. After heartbeat and respiration ceased, rats were monitored for a further 2 min to confirm death. Following euthanasia, liver tissue samples were collected for biochemical and histopathological evaluation.

Histopathological analysis

Tissue specimens were fixed in 10% formalin for 48 h at room temperature and subsequently embedded in paraffin blocks. Sections of 5 µm thickness were obtained and stained with hematoxylin for 10 min, followed by eosin staining for 5 min at room temperature. Histopathological evaluation and scoring were carried out using light microscopy (Nikon Corporation). All histological assessments were performed by the same pathologist in a blinded manner to ensure consistency and objectivity. Histopathological evaluation included scoring for hydropic degeneration, nuclear pleomorphism, neutrophil and lymphocyte infiltration, and focal necrosis, based on the criteria of Arslan et al. [14].

Biochemical analysis

Blood levels of alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), hemoglobin (Hgb), and hematocrit (Hct) were measured using standard biochemical methods to assess liver function and damage [16].

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) version 20.0. The Shapiro–Wilk test and Q–Q plot test were used to assess the data distribution. The results were analyzed using the Kruskal–Wallis test, followed by Dunn's test or one-way ANOVA and Tukey's test. The results were expressed as mean ± standard deviation (SD) and median (interquartile range [IQR]) values. Statistical significance was set at $p < 0.05$.

Results

Histopathological findings

Liver tissue hydropic degeneration differed significantly among the groups ($p = 0.001$). Hydropic degeneration was more pronounced in all groups compared to the control group ($p < 0.0001$). However, it was significantly lower in Group CeO_2 compared to Group S ($p = 0.045$). Neutrophil infiltration also varied significantly ($p = 0.003$), with Group CeO_2 showing markedly reduced infiltration compared to Group S ($p = 0.037$). Lymphocyte infiltration was elevated in all experimental groups relative to the control ($p < 0.0001$), but no statistically significant differences were observed between Groups S, CeO_2, and $S + CeO_2$. Necrosis and pleomorphism did not differ significantly between the groups ($p = 0.513$ and $p = 0.554$, respectively) (Figure 1, Table 1).

Significant differences in AST and LDH levels were detected among the groups ($p = 0.035$ and $p = 0.049$, respectively). Group S exhibited significantly higher AST levels than Group C ($p = 0.033$). Although AST levels in Groups CeO_2 and $S + CeO_2$ were lower than in Group S, the differences were not statistically significant ($p = 0.108$ and $p = 0.455$, respectively). Similarly, LDH levels were significantly higher in Group S compared to Group C ($p = 0.045$) but significantly lower in Group $S + CeO_2$ compared to Group S ($p = 0.012$). No significant differences were observed for ALT, Hgb, or Hct levels among the groups ($p = 0.429$, $p = 0.639$, and $p = 0.350$, respectively) (Table 2).

Discussion

This study investigated the protective effects of CeO_2 against liver damage induced by sevoflurane. The findings demonstrated that CeO_2 significantly reduced histopathological damage, particularly hydropic degeneration and neutrophil infiltration, in liver tissues. While AST and LDH levels were elevated in sevoflurane-administered rats, CeO_2 treatment mitigated these increases, although the reduction in AST was not statistically significant.

Sevoflurane has been considered a relatively safe anesthetic with low hepatotoxic potential. However, cases of hepatic necrosis and inflammation associated with its use suggest a multifactorial mechanism involving oxidative stress, immune reactions, and reactive metabolites like Compound A [17–19]. These findings align with previous studies, such as those by Nikoll et al., who reported acute and chronic liver damage following exposure to volatile anesthetics [20].

Antioxidant agents like CeO_2 have garnered attention for their ability to scavenge free radicals and mitigate oxidative stress-related damage. Studies by Manne et al. and Amin et al. have demonstrated the efficacy of CeO_2 in reducing hepatic damage in ischemia-reperfusion and oxidative stress models [21, 22]. Similarly, the present study observed a significant reduction in LDH levels in the $S + CeO_2$ group compared to the sevoflurane-only group, suggesting a protective effect on hepatic cell membranes.

In this study, although the histopathological benefits of CeO_2 were evident, its effects on biochemical markers such as ALT and AST, as seen in some studies [8, 23–25], were less evident. This may be attributed to the relatively low hepatotoxic potential of sevoflurane and the limited duration of exposure in this study. The findings

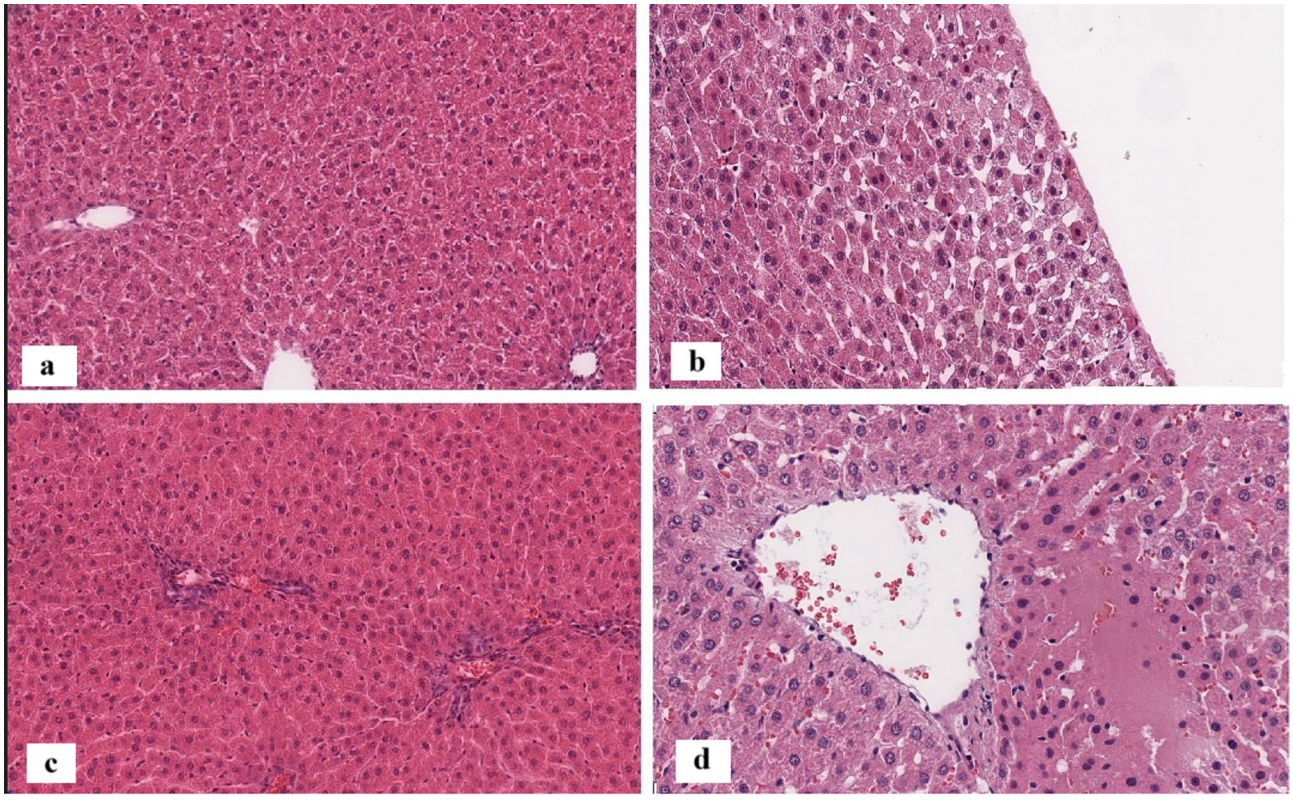

Fig. 1 Representative H&E-stained liver sections (x200 magnification):
(**a**) Group C: Normal hepatic architecture. (**b**) Group S: Ground-glass appearance in hepatocytes and nuclear pleomorphism. (**c**) Group CeO_2: Reduced hydropic degeneration, rare neutrophil and lymphocyte infiltration. (**d**) Group S + CeO_2: Mild hydropic degeneration, necrosis and pyknotic nuclei in damaged hepatocytes.

Table 1 Histopathological findings (hydropic degeneration, lymphocyte/neutrophil infiltration, necrosis, and pleomorphism) for each group

	Group C (*n* = 6)	Group S (*n* = 6)	Group CeO_2 (*n* = 6)	Group S + CeO_2 (*n* = 6)	*p*-value †
Necrosis	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.513
Pleomorphism	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.554
Hydropic degeneration	0.00 (0.00–0.00)	2.00 (1.75-2.00)*	1.00 (1.00–2.00)*. ‡	1.50 (1.00–2.00)*	0.001
Lymphocyte infiltration	0.00 (0.00–0.00)	2.00 (1.75-2.00)*	2.00 (1.75-2.00)*	2.00 (1.75-2.00)*	0.002
Neutrophil infiltration	0.00 (0.00–0.00)	1.00 (1.00-1.25)*	0.50 (0.00–1.00)*. ‡	1.00 (0.00–1.00)*	0.003

p-value †: The level of significance determined by Kruskal–Wallis test $p < 0.05$

*$p < 0.05$: compared to C group; ‡ $p < 0.05$: compared to S group

Table 2 Biochemical parameters (ALT, AST, LDH, Hgb, Hct) across groups

	Group C (*n* = 6)	Group S (*n* = 6)	Group CeO_2 (*n* = 6)	Group S + CeO_2 (*n* = 6)	*p*-value †
LDH (U/L)	484.66 ± 99.52	752.17 ± 21.09 *	640.83 ± 69.31	418.50 ± 118.86 ‡	0.049
ALT (U/L)	44.67 ± 1.36	61.67 ± 11.22	56.50 ± 16.18	56.33 ± 6.54	0.429
AST (U/L)	114.00 ± 13.20	296.17 ± 102.17*	143.33 ± 49.43	215.17 ± 36.19	0.035
Hgb (g/dL)	13.13 ± 0.33	13.33 ± 0.26	13.18 ± 0.27	12.43 ± 0.93	0.639
Hct (%)	39.30 ± 0.91	41.08 ± 1.13	39.67 ± 0.80	36.98 ± 2.69	0.350

p-value †: The level of significance determined by ANOVA test $p < 0.05$

*$p < 0.05$: compared to C group; ‡ $p < 0.05$: compared to S group

underscore the importance of histopathological evaluation alongside biochemical analysis to comprehensively assess hepatic damage.

The accumulation of CeO_2 in the liver and its stability at therapeutic doses suggest its suitability for mitigating oxidative stress in hepatic injury [26]. However, conflicting reports regarding its potential hepatotoxicity at higher doses necessitate careful dose optimization [15]. Future studies should investigate varying dosages, prolonged exposure durations, and subjects with pre-existing liver conditions to better understand the therapeutic potential of CeO_2 in clinical settings.

Conclusions

This study is of significance since it is the first experimental study on the effect of CeO2 on liver damage caused by sevoflurane. Some limitations of this study may be the duration of sevoflurane administration, the fact that the experimental group was composed of young male rats exposed to sevoflurane for the first time and examination of a limited number of parameters.

In conclusion, in this study, histopathological and biochemical changes in the livers of the sevoflurane group were detected and histopathologically a decrease in hydropic degeneration was observed in the groups that were administered CeO2. It is thought that further studies on CeO2 with experimental groups comprising subjects with different ages, sexes, and repeated exposure to sevoflurane in order to examine biochemical parameters of oxidative damage will yield more meaningful and positive results.

Abbreviations

ALT	Alanine Transaminase
AST	Aspartate Transaminase
CeO_2	Cerium Oxide Nanoparticles
H&E	Hematoxylin and Eosin
Hct	Hematocrit
Hgb	Hemoglobin
LDH	Lactate Dehydrogenase
ROS	Reactive Oxygen Species

Author contributions

Fazilet Erbay: Conceptualized the study, supervised the experiments, and contributed to manuscript writing, https://orcid.org/0000-0002-8764-5084. Levent Öztürk: Assisted in experimental design and contributed to manuscript writing, https://orcid.org/0000-0001-9755-033X. Merve Meryem Kıran: Performed histopathological evaluations, https://orcid.org/0000-0003-2498-0472. Gamze Gök: Conducted biochemical analyses and interpreted the results, https://orcid.org/0000-0002-2804-5548. Mustafa Arslan: Conducted statistical analysis, contributed to data interpretation, assisted in experimental design and animal handling, https://orcid.org/0000-0003-4882-5063. All authors read and approved the final manuscript.

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Data availability

"The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request. There are no ethical or legal restrictions on data sharing."

Declarations

Ethics approval and consent to participate

This study was approved by the Gazi University Experimental Animals Ethics Committee (Approval Code: G.Ü.ET-12.042, dated 08.07.2019).

Consent for publication

"Not Applicable".

Competing interests

The authors declare no competing interests.

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