The Effects of Sevoflurane and Desflurane on Hepatic Functions in Streptozotocin-Induced Diabetic Rats

Streptozotosin ile Diyabet Oluşturulan Ratlarda Sevofluran ve Desfluranın Karaciğer Üzerine Etkileri

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ABSTRACT

Objective: Diabetes mellitus (DM) is a common systemic disorder which is often encountered by anesthesiologists and associated with serious complications. Animal and clinical studies investigating the effects of volatile anesthetics and diabetes on organ functions are ongoing. In this study, we aimed to examine the histopathological and biochemical effects of sevoflurane and desflurane on hepatic functions in streptozotocin (STZ)-induced diabetic rats.
Materials and Methods: A total of 36 rats were randomly assigned into six groups: control group (Group C), diabetic control group (Group DC), desflurane group (Group D), sevoflurane group (Group S), diabetes-desflurane group (Group DD), and diabetes-sevoflurane group (Group DS). A single dose STZ 55 mg/kg was intraperitoneally injected to the diabetic groups. Diabetes was defined as having a blood glucose level of ≥250 mg/dL at 72 hours. At four weeks, desflurane 6% and sevoflurane 2% were administered in 100% oxygen over two hours. All anesthetized rats were administered intraperitoneal ketamine 100 mg/kg. Blood samples were collected from the abdominal aorta and all rats were sacrificed. Using the liver tissues, mean scores of injury (MSI) and the extent of Thiobarbituric Acid Reactive Substance (TBARS) were identified using and paraoxonase (PON) activities of anti-oxidant enzymes.
Results: Desflurane and sevoflurane increased MSI in the hepatic tissue; however, it did not reach a statistical significance. The MSI scores increased in diabetic rats compared to the control group. Desflurane and sevoflurane administration to the diabetic rats produced increased MSI scores, compared to the diabetic controls; however, it indicated no statistically significant difference. In the diabetic control group, TBARS increased, while PON decreased, compared to the control group. In the groups S and D, TBARS increased, while PON decreased, compared to the controls, suggesting no statistically significant difference. In the diabetic rats undergoing desflurane and sevoflurane administration, TBARS increased, whereas PON decreased.
Conclusion: Our study results show that desflurane and sevoflurane may lead to a mild to moderate hepatic injury in STZ-induced diabetic rats.

Key Words: Desflurane, sevoflurane, diabetes mellitus, liver, TBARS, PON.

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ÖZET

Amaç: Diyabetes Mellitus (DM), anestezistlerin sıklıkla karşılaştığı ve ciddi komplikasyonlarla ilişkili yaygın sistemik bir hastalıktır. Volatil anestezikler ve DM' nin organ fonksiyonları üzerindeki etkileri halen birçok klinik ve deneysel araştırmanın konusu olmaktadır. Bu çalışmada streptozosin (STZ) ile diyabet oluşturulan sıçanlarda sevofluran ve desfluranın karaciğer fonksiyonları üzerine histopatolojik ve biyokimyasal etkilerini incelemeyi amaçladık.
Yöntem: Toplamda 36 sıçan rastgele 6 gruba ayrıldı. Kontrol grubu (Grup K), Diyabet kontrol grubu (Grup DK), Desfluran grubu (Grup D), Sevofluran grubu (Grup S), Diyabet Desfluran grubu (Grup DD) ve Diyabet Sevofluran grubu (Grup DS). Diyabet oluşturulacak gruplara STZ 55 mg/kg tek doz intraperitoneal olarak uygulandı. Kan şekeri 72. saatte 250 mg/dL olarak saptanan sıçanlar diyabetik kabul edildi. Dört hafta sonunda minimum alveoler konsantrasyon ratlar için 1 olacak şekilde, desfluran %6 ve sevofluran %2 oranında 4 L/dk %100 oksijen içinde 2 saat süreyle uygulandı. Anestezi sonrasında tüm ratlara intraperitoneal ketamin (100 mg/kg) verilip abdominal aortadan kan alınarak ötenazi uygulandı. Ratların karaciğer dokusunda histopatolojik olarak ortalama hasar skorları (OHS), Tiyobarbitürik asit reaktif ürünlerinin (TBARS) değeri ve antioksidan eznimlerden paraoksonaz (PON) aktivitesi ölçüldü.
Bulgular: Desfluran ve sevofluran, karaciğer dokusunda OHS' yi artırdı; ancak istatistiksel olarak anlam kazanmadı. Kontrol grubuna göre diyabetik gruplarda OHS arttı. Diyabetik sıçanlara desfluran ve sevofluran uygulaması, diyabet kontrol grubuna kıyasla yüksek OHS oluşturdu; ancak istatistiksel olarak anlamlı bir farklılık gözlenmedi. Diyabet kontrol grubuna göre TBARS artarken PON aktivitesinde azalma gözlendi. Kontrol grubuna göre sevofluran ve desfluran gruplarında TBARS artarken PON azalmıştı ve istatistiksel olarak anlamlı bir fark olmadığı düşünüldü. Desfluran ve sevofluran uygulanan diyabetik sıçanlarda TBARS artarken PON azaldı.
Sonuç: Çalışma sonuçlarımız, desfluran ve sevofluranın STZ' ye bağlı diyabetik sıçanlarda hafif ile orta derecede karaciğer hasarına yol açabileceğini göstermektedir.

Anahtar Sözcükler: Desfluran, sevofluran, diyabetes mellitus, karaciğer, TBARS, PON.

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INTRODUCTION

It is established that volatile agents, which are commonly used in general anesthesia practice, may produce transient toxicities in the organism. The liver, in particular, is the organ that is most affected, as such agents are primarily metabolized in liver (1). In recent years, the incidence of sevoflurane- and desflurane-related hepatotoxicity has been increasing, as both agents have been widely used, thanks to their rapid onset of action and elimination profile in daily anesthesia practice (2,3).

The prevalence of diabetes mellitus (DM) is growing rapidly around the world and is a major cause of morbidity and mortality (4). Beacuse of rapid economic growth, increase in life expectancy, and changes in lifestyle, diabetes becomes one of the major public health issues also in Turkey and the crude prevalence of diabetes is 16.5 % (5). That's why anesthesiologists commonly encounter DM in clinical practice. It may result in abnormal liver enzymes, non-alcoholic fatty liver disease, cirrhosis, hepatocellular carcinoma, and acute hepatic failure (6).

Oxidative stress reflects an imbalance between the production of free oxygen radicals and a biological ability to detoxify their harmful effects. Long-lasting hyperglycemia increases oxidative stress, thereby, leading to several diabetic complications (7).

Animal and clinical studies investigating the effects of volatile anesthetics and diabetes on organ functions are ongoing. The current study aimed to examine the histopathological and biochemical effects of sevoflurane and desflurane on hepatic functions in streptozotocin (STZ)-induced diabetic rats.

MATERIALS and METHODS

Animals and experimental protocol

This study was conducted in the GUDAM Laboratory of Gazi University with the consent of the Experimental Animals Ethics Committee of Gazi University. All animals received human care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and the Use of Laboratory Animals" prepared by the National Academy of Science and published by the National Institutes of Health (NIH publication Nr. 85–23, revised in 1985).

In the study, 36 male Wistar Albino rats weighing between 250 and 350 g, raised under the same environmental conditions, were used. The rats were kept at 20-21ºC in cycles of 12 hours of daylight and 12 hours of darkness and had free access to food until two hours before the anesthetic procedure.

Before the procedure, the rats were randomly assigned into six groups: control group (Group C; n=6), diabetic control group (Group DC; n=6), desflurane group (Group D; n=6), sevoflurane group (Group S; n=6), diabetes-desflurane group (group DD; n=6), and diabetes-sevoflurane group (Group DS; n=6).

Diabetes was induced by a single intraperitoneal (IP) injection of STZ (Sigma Chemical, St. Louis, MO, USA) at a dose of 55 mg/kg body weight. The blood glucose levels were measured in all rats at 72 hours following the injection (GlucoDr Super Sensor, Allmedicus, Korea). Rats were classified as diabetic if their fasting blood glucose (FBG) levels exceeded 250 mg/dL and only those with a FBG of > 250 mg/dL were included in the diabetic groups (diabetes only, diabetes plus desflurane, and diabetes plus sevoflurane). The rats were kept alive for four weeks after STZ injection to allow the development of chronic diabetes.

At four weeks, all rats in the C and DC group were administered IP ketamine 100 mg/kg (Ketalar 50 mg/mL, Pfizer) and underwent median laparotomy. Blood samples were collected from the abdominal aorta and all rats were sacrificed. Liver tissues were obtained. The remaining four groups (Group S, Group D, Group DS, and Group DD) were anesthetized in a covered transparent glass container having an input and output hole of the anesthetic gas over two hours. Desflurane 6% (Suprane 240 mL, Baxter**)** and sevoflurane 2% (Sevorane 250 mL, Abbott, Istanbul, Turkey) were administered in 100% oxygen over two hours. Oxygen released 4 L/min from the pressurized oxygen tank through flowmeter was inserted to the volatile agent vaporizer. The mixture of the agent and 100% oxygen was delivered to the covered container using a line. At two hours following anesthesia, the rats were administered IP ketamine 100 mg/kg and underwent median laparotomy. Blood samples were collected from the abdominal aorta and all rats were sacrificed. Liver tissues were removed intact, avoiding any surgical trauma. Half of the liver tissue was fixed in 10% formalin for histopathological examination, while half of the tissue was frozen in liquid nitrogen and stored at -80°C for biochemical analysis.

Histological examination

Tissue samples were obtained by preserving the tissue unity without inflicting any trauma. The liver capsules of the rats were removed and fixed in 10% formalin solution and were sent for histopathological evaluation. The tissues were then embedded in paraffin blocks and sliced into 5µ sections. The sections were stained in hematoxylin eosin and were examined histopathologically under the light microscope.

In the histopathological examination, the scoring tables of Arslan et al. (8) were used (Table I). Each preparation was examined for hydropic degeneration (HD), nuclear polymorphism (NP), portal neutrophil infiltration (PNI), portal lymphocyte infiltration (PLI), and focal necrosis (FN), whereas the number of cases with histopathological injury (HDNC) was identified. For each preparation, total scores of hepatic injury (TSHI) for the pathologies listed in Table 1 were calculated and the mean scores of injury (MSI) were established.

Table 1: Histopathological changes scoring table in rat liver

Score Histopathological changes	0	1	2	3
HD	No Changes	10-20% of the cell	20-50% of the cell	More than 50% of the cell
NP	No Changes	10-20% of the cell	20-50% of the cell	More than 50% of the cell
PNI	No Changes	1-2 changes in portal area	3-5 changes in portal area	More than 6 changes in the portal area
PLI	No Changes	1-2 changes in portal area	3-5 changes in portal area	More than 6 changes in the portal area
FN	No Changes	1-2 changes in portal area	3-5 changes in portal area	More than 6 changes in the portal area

HD: Hydropic Degeneration, NP: Nuclear Polymorphism, PNI: Portal Neutrophile Infiltration, PLI: Portal Lymphocyte Infiltration, FN: Focal Necrosis.

Biochemical analysis

The liver tissues were first washed with cold deionized water to discard blood contamination and then homogenized in a homogenizator. Measurements on cell contest require an initial preparation of the tissues. The preparation procedure may involve grinding the tissue in a ground glass tissue blender using a rotor driven by a simple electric motor.

The homogenizator as a tissue blender similar to a typical kitchen blender is used to emulsify and pulverize the tissue (Heidolph Instruments GMBH&CO KGDiax 900 Germany®) at 1000 U for approximately 3 min. After centrifugation at 10 000 g for about 60 min, the upper clear layer was obtained.

The amount of malondialdehyde (MDA) was measured by thiobarbituric acid reactive substance (TBARS) analysis. According to the principle of the measurement method, two moles of thiobarbituric acid (TBA) are combined with one mole of MDA at 85-100 C in acidic medium and the purple TBA-MDA complex is formed. The absorbance of this complex is measured spectrophotometrically. The paraoxonase-1 (PON-1) enzyme catalyzes the cleavage of p-nitrophenol and acetic acid of paraoxon, and the absorbance of p-nitrophenol formed at the end of the reaction is measured spectrophotometrically.

Statistical analysis was performed using SPSS v12.0 software (SPSS Inc., Chicago, IL, USA). Sample size was predetermined using a power analysis: α=0.05 and power of 0.8 (SD: 1.22, mean difference: 2.28,normal two-sided test). Difference in hepatic injury scores was used to determine sample size.

The analysis showed that 6 rats per group would be sufficient. A *p* value <0.05 was considered statistically significant. Demographic data were expressed in mean±standard deviation. All other values were presented in mean±standard error, n (%). The data were analyzed using the Kruskal-Wallis variance analysis.

The variables with significance were evaluated through the Bonferroni-adjusted Mann-Whitney U-test. The chi-square and Fisher's exact chi-square test were used to compare the data among the groups.

RESULTS

The weight of the rats was similar among all groups before diabetes induction. However, diabetic rats had a significantly lower weight compared to the other rats (p<0.0001). Compared to the baseline values, diabetic rats had a significantly lower weight after diabetes induction (p<0.0001) (Table 2).

Blood glucose levels were similar in all rats before diabetes induction. However, diabetic rats had significantly increased blood glucose levels compared to the other rats (p<0.0001). Compared to the baseline values, diabetic rats had significantly higher blood glucose levels after diabetes induction (p<0.0001) (Table 2).

Table 2: The demographic data and blood glucose values of the rats in the study (Mean ± standard deviation)

Data	Time	Group C (n=6)	Group DC (n=6)	Group S (n=6)	Group D (n=6)	Group DS (n=6)	Group DD (n=6)	P**
Weight (gr)	Before diabetes induction	233.8±13.9	212.5±17.7	217.5±21.2	221.8±8.4	230.7±47.5	219.0±10.4	0.415
	After diabetes induction	240.8±15.9	178.7±23.7*,+,&,#	223.5±13.0	228.0±10.3	180.2±13.5*,+,&,#	186.8±6.8*,+,&,#	<0.0001
Blood Glucose Values (mg/dL)	Before diabetes induction	94.8±5.7	99.2±6.5	91.0±8.5	93.2±7.4	94.7±9.8	95.7±10.1	0.655
	Three days later	94.8±5.7	333.0±60.6*,+,&,#	91.0±8.5	93.2±7.4	382.5±67.4*,+,&,#	428.3±58.9*,+,&,#	<0.0001

Group C: Control Group, Group DC: Diabetes Control Group, Group S: Sevoflurane Group, Group D: Desflurane Group, Group DS: Diabetes-Sevoflurane Group, Group DD: Diabetes-Desflurane Group.

** p<0.05: Kruskal-Wallis test with multiple comparisons; * p<0.05: Compared with Group C; + p<0.05: Compared with Group S; & p<0.05: Compared with Group D; # Compared with Group Initial value

Mild histopathological injury was observed in three rats in the Group C (50%) and five rats in the Group DC (100%). Six rats in the Group D (100%) and four rats in the Group S had mild histopathological alterations.

When non-diabetic groups were examined, it was found that sevoflurane and desflurane applications increased MSI according to the control group, but this increase was not statistically significant. In the diabetic groups (group DC, DS, DD), MSI was significantly higher than control group.

When diabetic groups were compared among themselves, MSI was increased in diabetic groups treated with desflurane and sevoflurane (groups DD and DS) compared to diabetes control group, but this increase was not statistically significant (Table 3, Fig 1) (Group C-Group DC: p=0.049; Group C-Group DS: p=0.049; Group C-Group DD: p=0.020).

Although desflurane and sevoflurane increased MSI scores in diabetic groups (Group DS and DD) compared to the Group DC, there was no statistically significant difference in the MSI scores between the Group DD and Group DC (Table 3, Fig 1).

Table 3: Histopathological data of rat liver damage detected (mean ± standard error, n(%))

Group	Group C (n=6)	Group DC (n=5)	Group S (n=6)	Group D (n=6)	Group DS (n=5)	Group DD (n=6)
Data of Histopathology						
HD	0	4	2	1	5	6
NP	0	3	1	1	3	6
PNI	0	0	0	0	0	0
PLI	3	5	4	6	5	6
FN	2	5	2	5	5	5
TSHI	**5**	**17**	**9**	**13**	**18**	**23**
MSI	**1.00±0.63**	**4.00±1.14**	**1.80±0.66**	**2.60±1.21**	**4.00±1.14**	**4.60±1.17**

HD: Hydropic Degeneration, NP: Nuclear Polymorphism, PNI: Portal Neutrophile Infiltration, PLI: Portal Lymphocyte Infiltration, FN: Focal Necrosis, TSHI: Total Scores of Hepatic Injury, MSI: Mean Scores of Injury.

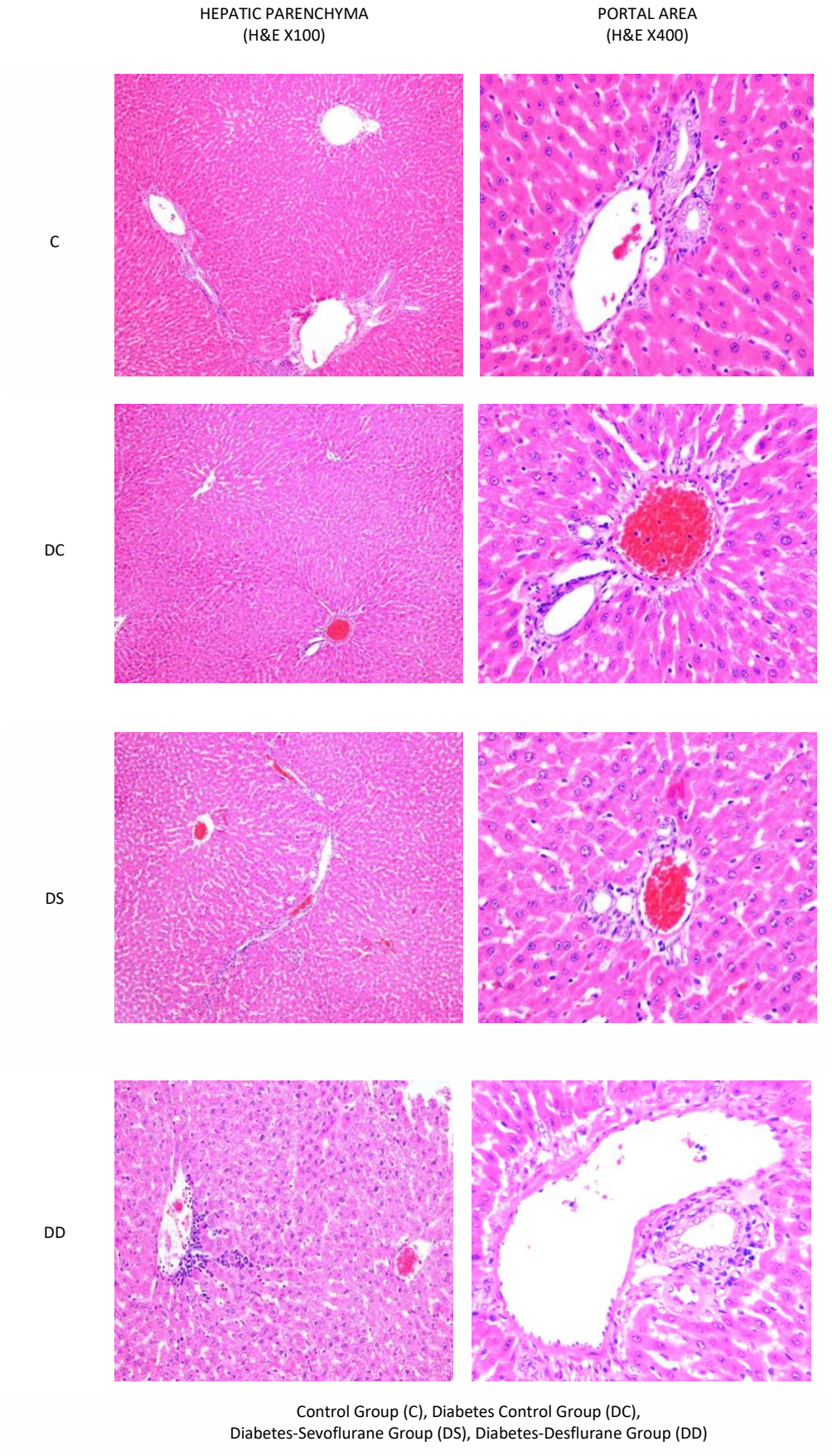

Figure 1: Hepatic parenchyma and portal area of liver

In addition, there was no significant difference in the HD, NP, PNI, and FN values between the non-diabetic rats and controls (Table 3).

The rats in the Group DD and DS had significantly higher HD values (Group C-Group DC: p=0.003; Group C-Group DS: p<0.0001; Group C-Group DD: p<0.0001) (Fig 2) and FN values (Group C-Group DC: p=0.049; Group C-Group DS: p=0.003; Group C-Group DD: p=0.003) (Table 3, Fig 2), compared to the Group C.

Furthermore, Group DD and Group DS had significantly higher HD values, compared to the Group DC (Group DC-Group DS: p=0.004; Group DC-Group DD: p<0.0001) (Table 3, Fig 2).

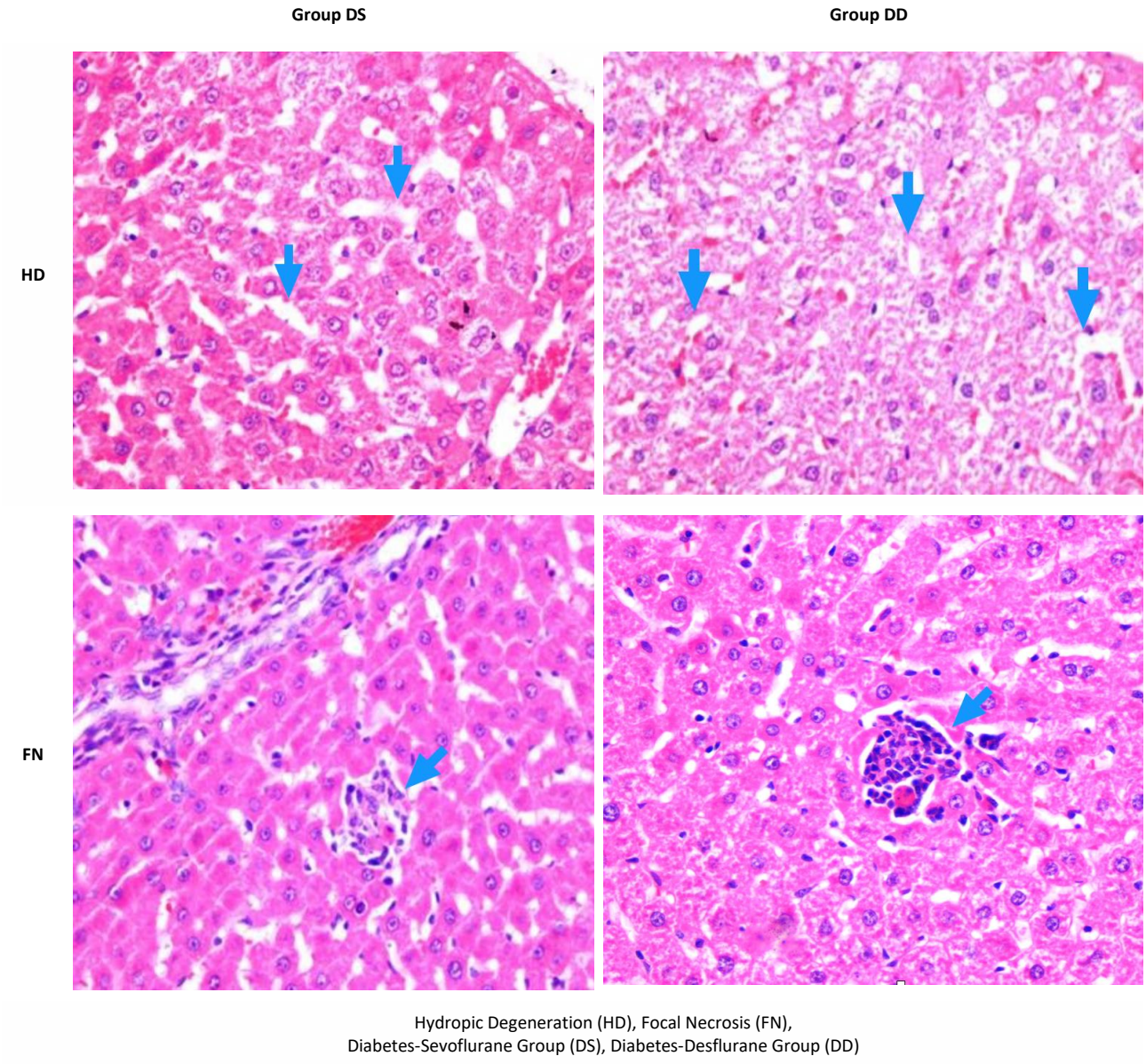

Figure 2: HD and FN in diabetic groups of sevoflurane and desflurane

Similarly, desflurane and sevoflurane significantly increased NP values (Group C-Group DC: p=0.015; Group C-Group DS: p=0.015; Group C-Group DD: p<0.0001) and PLI values among the diabetic rats (Group C-Group DC: p=0.015; Group C-Group DS: p=0.015; Group C-Group DD: p=0.011), compared to the Group C (Table 3).

In the diabetic rats undergoing desflurane and sevoflurane administration, there was no significant difference in NP, PLI, PNI, and FN values, compared to the diabetic controls (Table 3). None of the rats had PNI injury (Table 3).

There was a significant difference in TBARS values among the groups (p<0.0001).

These values were significantly higher in Group DC, Group DS and Group DD, compared to Group C (p=0.008, p<0.0001, p<0.0001). In addition, Group S and D had also increased TBARS values; however, there was no statistical significance (Table 4).

There was a significant difference between the groups in terms of PON enzyme activity of the liver tissues (p=0.033). PON enzyme activity was significantly lower in Group DS and DD than in control group (p=0.006 and p=0.005, respectively). Although PON enzyme activity was lower in the other groups than the control group, it was not statistically significant (Table 4).

Table 4. Oxidant status parameters of liver tissue of rats [Mean ± standard deviation]

Groups Oxidant Parameters	Group C (n=6)	Group DC (n=6)	Group S (n=6)	Group D (n=6)	Group DS (n=6)	Group DD (n=6)	P**
MDA (nmol/mg.pro) (TBARS method)	0.05±0.02	0.09±0.02*	0.08±0.03	0.07±0.02	0.12±0.02*	0.12±0.04*	<0.0001
PON (IU/mg.pro)	601.1±447.5	389.8±123.4	467.2±192.1	429.3±331.5	176.6±79.2*	164.9±68.5*	0.033

MDA: Malondyaldehyde, TBARS: Thiobarbituric Acid Reactive Substance, PON: Paraoxonase
** p<0.05: Kruskal-Wallis test with multiple comparisons; * p<0.05: Compared with Group C

DISCUSSION

In the present study, we observed a mild to moderate histopathological hepatic injury in the rats that were administered desflurane and sevoflurane. We also detected mild histopathological hepatic injury in the STZ-induced diabetic rats. Although the extent of the injury was larger in the desflurane group, inhalation agents that were used triggered mild to moderate hepatic injury in the diabetic rats.

As with halothane, desflurane is metabolized in the liver with CYP enzymes. As a result, desflurane-related hepatotoxicity is similar to enflurane, isoflurane, and halothane, but is rarer. Desflurane-related hepatotoxicity has been noted in the literature in recent years (3).

Sevoflurane is rapidly metabolized in the liver and its metabolites bind to hepatic proteins. Therefore, sevoflurane-related hepatotoxicity is considered to be multifactorial rather than an immunogenic mechanism. Compound A induces immune response and leads to hepatocyte injury, by increasing the cytosolic free calcium and free radicals. In recent years, the incidence of sevoflurane-related hepatotoxicity has been increasing (9).

Increased hepatic enzymes are the gold standard in the diagnosis of anesthesia-induced hepatotoxicity; however, the presence of aminotransferases in certain organs other than liver decreases the diagnostic specificity. We used histopathological examination for the definite diagnosis of hepatotoxicity rather than aminotransferase analysis, as the latter may limit the diagnosis (8). In a study investigating the histopathological effects of halothane and sevoflurane on hepatic tissues in rats, Saubhia et al. (10) demonstrated that sevoflurane did not cause microscopic injury of the liver parenchyma, compared to halothane. In the present study, we observed no significant difference in histopathological HD, NP, PLI, PNI, and FN values between the sevoflurane group and controls, in consistent with the study findings of Saubhia et al. (10). However, there was a statistically non-significant increase in MSI scores in the sevoflurane group, compared to the controls.

Although the recommended STZ dose for experimental diabetes induction in rats is 35 to 65 mg/kg (11). In our study, we administered STZ at a dose of 55 mg/kg, which is within the normal range. Consistent with the literature data, blood glucose level was higher in the STZ-induced diabetic rats (Group DC, Group DS, and Group DD) on day 3 following injection, compared to the controls. Therefore, we believe that STZ 55 mg/kg is adequate to induce diabetes in rats.

In a study using STZ 65 mg/kg to induce diabetes in rats, Arslan et al. (12) reported that four diabetic rats died. The authors concluded that death events might be related to the high-dose STZ administration and that a lower dose might be used to induce experimental diabetes. Another major cause of death within 24 hours is transient hypoglycemic phase 4 to 8 hours following STZ injection in experimental diabetic rat models (13). Based on these data, we used STZ at a recommended dose to minimize mortality and 5% glucose solution was added to the drinking water within 24 hours. Despite all measures taken, one rat in the Group DC and one rat in the Group DS died. These death events can be attributed to the sudden onset of hyperglycemia and ketoacidosis. Mortality can be reduced by intensive blood glucose control and regular insulin therapy.

Hepatocellular changes occur in liver tissues after the formation of diabetes in rats. These changes are deterioration in the radial placement of hepatocytes starting from the central veins towards the periphery and hydropic change in hepatocytes located at the periphery of the lobules, generating inflammation, necrosis and vacuolisation in hepatocytes (14).

Consistent with the literature data, we demonstrated mild HD, PLI, and FN in the hepatic tissue among the diabetic rats. These findings suggest that diabetes, even at an early stage, may yield tissue injury, as confirmed histopathologically.

Lipid peroxidation is one of the most sensitive indicators of cellular oxidative response. MDA is formed as an end product of lipid peroxidation and generated by the decomposition of polyunsaturated fatty acids (15). Studies using desflurane and sevoflurane showed MDA might widely vary. In clinical study Sivaci et al. (16) examined the effects of sevoflurane and desflurane on oxygen radicals in patients undergoing laparoscopy. The authors reported a statistically significant increase in the MDA levels in the patients receiving sevoflurane compared to the control subjects, while MDA was higher in desflurane receivers compared to the sevoflurane group. In addition, Ceylan et al. (17) compared the oxidant and anti-oxidant effects of desflurane and propofol and reported a higher MDA level in the desflurane group. Consistent with the study findings of Sivaci et al. (16), we showed increased MDA levels in the sevoflurane group; however, it did not reach statistical significance. Similar to the study findings of Ceylan et al. (17), we also observed a statistically non-significantly higher level of MDA in the desflurane group.

Lipid peroxidation is one of the main drivers of cellular damages and the elevated levels of oxidative stress in diabetics are due to autoxidation of glucose, protein glycation, lipid peroxidation, and low activities of antioxidant enzymes (18). Although non-specific, several studies have shown that MDA increase is associated with the degree of lipid peroxidation. Hamadi et al. (19) found increased MDA levels in the hepatic tissues in STZ-induced diabetic rats compared to the controls. In a clinical study, Aouacheri et al. (20) examined the possible relationship between lipid peroxidation and diabetes. The authors found increased MDA levels in 59 type 2 diabetic patients of both sexes, compared to the control subjects. Consistent with the literature data, we observed a significant increase in the MDA enzyme activity in diabetic rats compared to non-diabetic rats. Although MDA enzyme activity remarkably increased in diabetic rats receiving desflurane or sevoflurane compared to the controls, it was similar to the level of diabetic controls. These findings indicate that inhalation agents are not statistically significantly associated with increased lipid peroxidation in diabetes.

Paraoxonase, which is a natural anti-oxidant enzyme, is abundant in the liver and plasma in rats. It is synthesized and released by the liver and is reported to be reduced in acute and chronic hepatic diseases (21). In our study, desflurane and sevoflurane administration reduced the PON enzyme activity; however, there was no statistical significance. Despite reduced activity, consistent results among the groups may be explained by the severity of the hepatic injury (mild).

In a study Wójcicka et al (22) investigated the effects of metformin on serum PON enzyme activity in STZ induced diabetic rats. The authors reported reduced activity in the diabetic rats, compared to the non-diabetic controls. A clinical study conducted by Kopprasch et al. (23) found no significant difference in the PON-1 enzyme activity between the patients with normal or impaired glucose tolerance and newly diagnosed early diabetes. In consistent with the previous studies of Kopprasch et al. (23), we observed no significant difference in the PON enzyme activity in between the diabetic rats and control group. Based on these results, we conclude that early diabetes may disrupt the anti-oxidant balance; however, anti-oxidant activity remains. We also showed that the PON enzyme activity remained unchanged following the anesthetic administration in diabetic rats, compared to Group DC. However, we observed a significant increase in the PON enzyme activity in diabetic rats, compared to Group C.

Furthermore, hepatic injury may not only result from the direct effects of inhalation agents or its metabolites, but also from traumatic causes, use of hepatotoxic agents, hypoxia, infectious diseases, sepsis, pregnancy, and nutritional defects (24). During anesthesia, several mechanisms are responsible for reduced functional capacity and impaired oxygenation. Inhalation agents, at sub-anesthesic doses, may also contribute to these adverse conditions, inhibiting the hypoxic ventilatory response (25).

In the present study, we administered both inhalation agents at 100% oxygen concentration to prevent hypoxia and we did not perform an additional surgical procedure. Also, we did not use any agent that may induce enzyme activity and not limit dietary intake. Therefore, we eliminated all factors that might cause hepatotoxicity in our study.

Despite everything in this study, there were some limitations. First of all, the smallest number that could be taken in the direction of the ethics committee decision had to be studied. Although the sample size was sufficient, the groups were formed with few rats. We think that statistically more meaningful results can be achieved with groups to be formed with more animals. For this reason, we believe that further large-scale studies are required to assess the effects of these inhalation agents on hepatic functions thoroughly and to establish a decision. The second limiting factor is that the ventilation of the rats is spontaneous and cardiac monitoring is not possible. In addition to the anesthesia method in study, no invasive procedure or monitoring technique was used because no surgical procedure was performed.

In conclusion, our study results show that desflurane and sevoflurane may lead to a mild to moderate hepatic injury in STZ-induced diabetic rats.

Conflict of interest

No conflict of interest was declared by the authors.

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