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The Renoprotective Effects of Desflurane and Sevoflurane in Lower Limb Ischemia-Reperfusion Injury on Streptozotocin-Induced Diabetic Rats

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Abstract: The study aims to determine the protective effects of sevoflurane and desflurane on the kidneys in lower limb ischemia-reperfusion injury (IRI) streptozotocin-induced diabetic rats. Thirty Wistar rats were randomly divided into equal five groups. The control (group C), diabetes-control (group DC), Diabetes-I/R (group DIR), Diabetes-I/R-sevoflurane (group DIRS), Diabetes-I/R-desflurane (group DIRD). 55 mg/kg Streptozotocin was administered intraperitoneally to diabetic groups as a single dose. 72nd hours were considered diabetic blood glucose 250 mg/dl or above, and at the end of 4 weeks, all groups underwent laparotomy. In groups C and DC, there was no further action. In the group, DIR was performed 2 hours in the infrarenal abdominal aorta in order clamped be put and remove. Sevoflurane and desflurane were administered so that the minimum alveolar concentration was one during the ischemia and reperfusion periods. At the end of the reperfusion period, kidney tissues were taken for biochemical and histopathological examinations. In the DIR group, Nitric oxide synthases (NOS) enzyme activity was observed significantly higher than C and DC groups. In DIRS and DIRD groups, it was significantly lower than DIR. TBARS level is significantly higher in all groups compared to group C. In the DIR group, the TBARS level was significantly higher than in the DC group. In DIRS and DIRD groups, it was significantly lower than DIR. DIR group Superoxide dismutase (SOD) enzyme activity was observed significantly higher than C and DC groups. In DIRS and DIRD groups, it was significantly lower than DIR. These results demonstrate that sevoflurane and desflurane have protective effects on the kidneys in lower limb IRI on streptozotocin-induced diabetic rats. © 2021 NTMS.

Keywords: Ischemia-Reperfusion, Sevoflurane, Desflurane, Kidney.

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1. Introduction

Nowadays, ischemia-reperfusion injury (IRI) is occurred routinely with different methods such as vascular clamps or tourniquet applications to provide bleeding control in many surgeries from major vascular surgeries such as aortic dissection (1) to extremity surgery (2). Besides, IRI occurs in many clinical conditions such as myocardial and cerebrovascular infarctions, thrombolytic therapy, cardiopulmonary resuscitation, and hemorrhagic shock.

Ischemia-reperfusion injury is a paradox with cellular dysfunction and death following blood flow restoration to ischemic tissues (3). Restoring blood flow is essential for the recovery of tissues from ischemia. Following reperfusion, do not return to standard terms. Instead, it also increases damage by activating various immune system responses and cell death programs (4). It can lead to multi-system organ failure by causing systemic damage to the ischemic organ itself and distant organs such as the kidney (5).

Diabetes mellitus (DM) is a metabolic disease with high levels of blood glucose. Nephropathy and vasculopathy are common in the long period of the disease. It is also an independent risk factor among the causes of acute kidney injury (AKI) (6). It was increased in diabetic patients undergoing surgery (7), with sepsis/septic shock (8), and even without precipitating events (9). It has also been clearly shown to aggravate IRI-induced kidney damage (10).

Reno-protective effects of various agents such as xenon (11), statin (12), lithium (13) in IRI have been investigated. Although anesthetic agents such as dexmedetomidine (14) and isoflurane (15) have been studied, there is no standardized anesthesia protocol.

This study aimed to investigate the renoprotective effects of desflurane and sevoflurane in lower limb IRI on diabetic rats.

2. Material and Methods

This study was performed after the Experimental Animals Ethical Committee approve of Gazi University, dated 27.11.2013, and code number "G.Ü. ET-13.074".

The research was done in Gazi University Experimental and Clinical Research Center (GUDAM). For this research, in the range of 250 and 350 g, 30 Wistar albino rats were used, which are raised under the same environmental provisions. The rats were exposed to cycles of 12h daylight and 12h darkness and reached food until 2h before anesthesia was given. Six healthy rats were a control group (C). The other rats were split as diabetic control (DC), diabetic ischemia-reperfusion (DIR), diabetic ischemia-reperfusion, and sevoflurane (DIRS), diabetic ischemia-reperfusion, and desflurane (DIRD) into four groups randomly. Streptozotocin (STZ) was used for treatment and prepared just before the treatment. After three days of applying STZ, the glucose levels were evaluated, and the rats were classified as diabetic, which glucose (FBG) levels are over 250mg/dl. Before applying sevoflurane and desflurane, the rats were observed for four weeks to have chronic diabetes after the STZ injection (16). The vaporizers were adjusted to be desflurane 6% and sevoflurane 2% for the target minimum alveolar concentration (MAC) 1. The anesthesia protocol was administered in a wide transparent plastic box. The box was integrated into a semi-open anesthesia device with static hoses. Anesthetics were driven into the box with 100% oxygen flow of 6 lt/min for 4 hours. The control group (C), the Diabetic control group, and the DIR group had no administration. After shaving the abdomen, all rats were positioned supine on the operating table. A median laparotomy was applied after cleaning the abdomen region with 1% polyvinylidene and covered with a drape. The infrarenal aorta blood flow stopped with an atraumatic clamp for two hours. Afterward, the clamp was removed, and blood flow was maintained for 2 hours. Inhalation anesthesia was maintained during the ischemia and perfusion periods. After the reperfusion period, histopathological and biochemical assessment of kidney specimens were completed.

2.1. Histopathological Evaluation

Histopathological assessment was studied in the Department of Histology at Kirikkale University. After the fixation process, specimens were prepared with paraffin blocks. Tissue sections of 5 μ were stained via hematoxylin and eosin (H&E). As defined by Bostan et al. (17), the histopathological assessment and scoring were performed under light microscopy. Tubular cell spillage (TCS), tubular dilatation (TD), lymphocyte infiltration (LI), Bowman space dilatation (BSD), tubular cell degeneration and necrosis (TCDN), tubular hyaline cylinder (THC), vascular vacuolization and hypertrophy (VVH), and Glomerular vacuolization(GV) were classified via a scoring system: 0: no change; +1: minimal; +2: medium; +3: severe change.

2.2. Biochemical Evaluation

The biochemical examination was conducted in the Department of Medical Biochemistry at Gazi University. The level of malondialdehyde (MDA), an indicator of lipid peroxidation and oxidative stress in kidney tissue, was evaluated by measuring the Thiobarbituric acid reactive substance (TBARS) level. Besides, Nitric oxide synthase (NOS), Glutathione transferase (GST), Catalase (CAT), and Superoxide Dismutase (SOD) enzyme activities measurements were performed. NOS, GST, CAT, and SOD assays were administered as defined by Aebi, Habig, and Durak (18-20). $NBTH_2$ occurs with the reduction of NBT. The amount of enzyme that caused 50% inhibition of NBTH2 absorbance at 560 nm was defined as SOD activity. The decrease in absorbance at 240 nm due to the consumption of H2O2 forms the basis

of the CAT activity method. The GST activity is assessed by measuring the GSH-CDNB complex at 340 nm. Sulfanilic acid is diazotized with nitric oxide at acid pH and binds to N-(1-naphthyl-ethylene diamine). The empty tube absorbance at 540 nm is compared with the sample tube's absorbance, thereby measuring the NOS activity. The TBARS examination was performed via the thiobarbituric acid (TBA) method to establish lipid peroxidation (21). TBARS determine carried out based on the TBA-MDA reaction, which constitutes a pink pigment with maximum absorption at 532 nm in acid pH. The 1,1,3,3-tetra ethoxy propane was defined as a standard MDA solution. TBARS levels and enzyme activities were monitored using a Shimadzu UV-1601 spectrophotometer based on endpoint change in absorbance at 25 °C. Results were announced U/mg protein and mIU/mg protein for SOD and GST, respectively. NOS and CAT results were expressed IU/mg protein. Results of TBARS levels were as nmol/mg protein.

2.3. Statistical analysis

We performed the statistical analysis with the SPSS 20.0 (IBM, Armonk, New York, USA) packet program. P values less than 0.05 were considered statistically significant. Data were presented as Mean±Standard Error Mean. Kruskal–Wallis variance analysis was used for the evaluation of data. The Mann-Whitney U test with Bonferroni correction was used in the analysis of significant variables.

3. Results

3.1. Histopathological Findings

In histopathological examination showed a significant difference in GV level between all study groups (p=0.022). GV was more common in DIR groups compared to the control group (p=0.001). The decrease in GV in the DIRD group was significant compared to the DIR group (p=0.023) (Table 1, Figure 1-5).

The TD difference between the groups was significant (p=0.007). The increase in TD was significant in the DIR group compared to the control group and the DC group (p<0.0001, p=0.034, respectively) (Table 1, Figure 1-5).

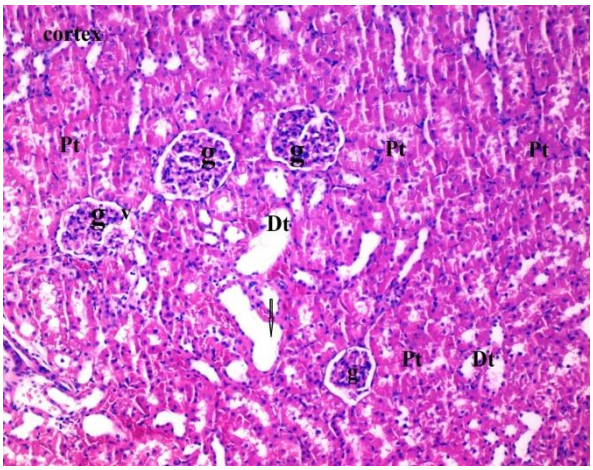

Figure 1: Control group kidney tissue (Pt: Proximal tubule, Dt: Distal tubule, g: glomerule, arrow: dilated tubule, v: vacuole) (H&EX10).

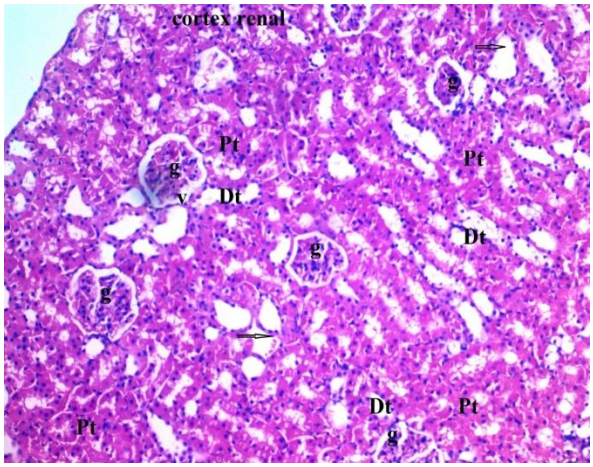

Figure 1: Diabetes Control group kidney tissue (Pt: Proximal tubule, Dt: Distal tubule, g: glomerule, arrow: dilated tubule, v: vacuole) (H&EX10).

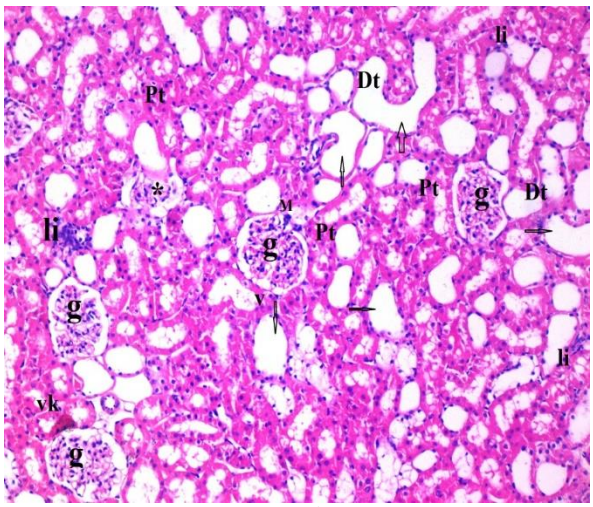

Figure 2: Diabetes ischemia reperfusion group kidney tissue (Pt: Proximal tubule, Dt: Distal tubule, v: vacuole, Li: Lymphocyte infiltration, g: glomerule, *: degenerate glomerule, arrow: dilated tubule, vk: vascular congestion) (H&EX10).

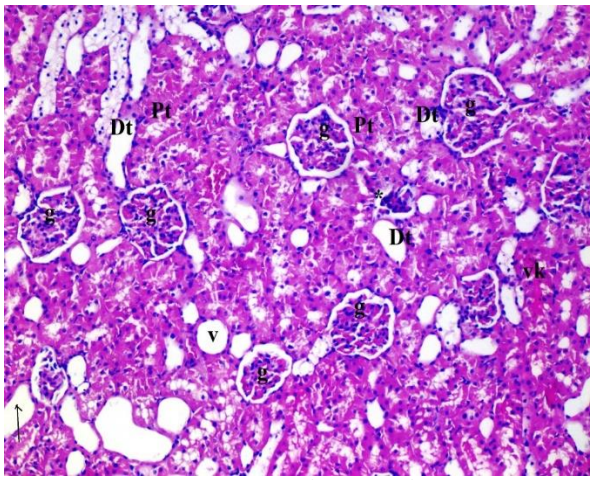

Figure 4: Diabetes ischemia reperfusion sevoflurane group kidney tissue (Pt: Proximal tubule, Dt: Distal tubule, g: glomerule, v: vacuole, arrow: dilated tubule, *: degenerate glomerule, vk: vascular congestion) (H&EX10).

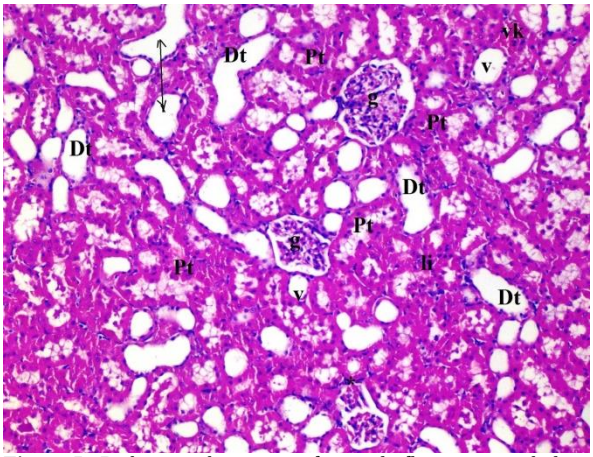

Figure 5: Diabetes ischemia reperfusion desflurane group kidney tissue (Pt: Proximal tubule, Dt: Distal tubule, g: glomerule, v: vacuole, arrow: dilated tubule, *: degenerate glomerule, vk: vascular congestion) (H&EX10).

There was a significant difference in the VVH level between the groups (p<0.021). VVH was more common in the DC and DIR groups than the control group (p=0.030, p=0.008, respectively). Besides, it was significantly lower in the DIRD group than in the DIR group (p=0.008) (Table 1, Figure 1-5).

THC was found to be significantly different between groups (p=0.013). THC was more common in the DIR group than the control and DC groups (p=0.001, p=0.006, respectively). Besides, it was found that the DIRS and DIRD groups were significantly lower than the DIR group (p=0.025, p=0.006, respectively) (Table1, Figure 1-5).

The LI difference was significant between the groups (p=0.046). It was more common in the DIR group than in the control group (p=0.008). It was also significantly lower in the DIRS group than in the DIR group (p=0.008). There was a significant difference in LI between the groups (p=0.046). LI was more common in the DIR group than in the control group (p=0.008). It was also significantly lower in the DIRS group than in the DIR group (p=0.008) (Table 1, Figure 1-5).

THDN, BSD and THD were similar between groups (p=0.108, p=0.113, p=0.097, respectively), (Table 1, Figure 1-5).

3.2. Biochemical Findings

In the biochemical examination, when the groups were compared in terms of serum GST enzyme activity, there was significant (p<0.0001). GST enzyme activity was significantly higher in DC, DIR, DIRS, and DIRD groups than in the C group (p<0.0001, all). Similarly, it was significantly higher in DIR groups than in the DC group (p<0.0001, p=0.001, p=0.006, respectively). Also, it was found to be significantly lower in the DIRS and DIRD groups compared to the DIR group (p=0.030, p=0.006, respectively) (Table 2).

There was a significant difference in serum CAT enzyme activity between the groups (p=0.003). CAT enzyme activity was significantly higher in the DIR group than the C and DC groups (p<0.0001, p=0.024, respectively). It was also found to be significantly lower in the DIRS and DIRD groups compared to the DIR group (p=0.003, p=0.006, respectively) (Table 2).

When the groups were compared with each other in terms of serum NOS enzyme activity, there was a significant difference between them (p=0.043). NOS enzyme activity was significantly higher in the DIR group than the C and DC groups (p=0.006, p=0.021, respectively). Besides, it was found to be significantly lower in the DIRS and DIRD groups compared to the DIR group (p=0.027, p=0.017, respectively) (Table-2).

There was a significant difference in serum TBARS level between the groups (p<0.0001). TBARS level was significantly higher in all groups than in group C (p=0.002, p<0.0001, p=0.009, p=0.042, respectively). Similarly, it was significantly higher in the DIR group than the DC group (p=0.004). Also, it was found to be significantly lower in the DIRS and DIRD groups compared to the DIR group (p<0.0001, p=0.001, respectively) (Table 2).

When compared in terms of SOD enzyme activity, there was a significant difference between the groups (p<0.0001). SOD enzyme activity was significantly higher in the DIR group than the C and DC groups (p<0.001, p=0.003, respectively). Besides, it was found to be significantly lower in the DIRS and DIRD group compared to the DIR group (p<0.0001, p<0.0001, respectively) (Table 2).

4. Discussion

Ischemia/reperfusion injury can describe as restriction of blood flow to a tissue followed by restoration of blood supply and re-oxygenation. The fatal damages can occur during organ transplantation, sepsis, and infarctions. Under these conditions, tissue injury increases via inflammation cascade elements such as over leukocytes activation, cytokines, and reactive oxygen species (22, 23). IRI's effects on the kidney can be explained by AKI, which can result in rapidly progressive dysfunction and result in mortality (24, 25). It has been reported that more than 10 million patients develop AKI each year, and nearly 2 million of them die (26).

There is a direct relationship between the severity of IRI and the levels of antioxidant defense system elements such as SOD, CAT, GST, MDA, and NOS. Oxidoreductases constitute the most important free radical scavenging systems exemplified by CAT, SOD, and Glutathione peroxidase (GSH-Px) and play a cell-protective role beyond antioxidant function (27). High blood levels of CAT show antioxidant activity (28). High GST activity is considered a marker for the elimination of metabolites associated with peroxidation (29). Malondialdehyde is a stable product created by the peroxidation of polyunsaturated fatty acids. It shows the peroxidation of the cell wall. The tissue and plasma MDA levels are well-known indicators of systemic response and oxidative stress after the IRI (30). An idea about the degree of membrane damage can be obtained by measuring the MDA level (31).

Table 1: Histopathological findings of kidney tissue (Mean±SEM).

	Group C (n=6)	Group DC (n=6)	Group DIR (n=6)	Group DIRS (n=6)	Group DIRD (n=6)	P**
Glomerular vacuolization (GV)	0,33±0,21	0,83±0,17	1,33±0,21*	0,83±0,17	0,67±0,21&	0,022
Tubular dilatation (TD)	0,33±0,21	1,00±0,00	1,83±0,31*,?	0,83±0,31&	0,67±0,33&	0,007
Vascular vacuolization and hypertrophy (VVH)	0,33±0,21	1,00±0,00*	1,17±0,17*	0,83±0,31	0,50±0,21&	0,021
Tubular cell degeneration and necrosis (TCDN)	0,33±0,21	0,67±0,21	1,00±0,00	0,50±0,22	0,33±0,21	0,108
Bowman space dilatation (BSD)	0,00±0,00	0,33±0,21	0,67±0,21	0,17±0,17	0,50±0,21	0,113
Tubular hyalin cylinders (THC)	0,17±0,17	0,33±0,21	1,17±0,17*,?	0,50±0,22&	0,33±0,21&	0,013
Lymphocyte infiltration (LI)	0,33±0,21	0,67±0,21	1,17±0,17*	0,67±0,21	0,33±0,21&	0,046
Tubular cell spill (TCS)	0,50±0,22	1,00±0,00	1,00±0,00	0,67±0,21	0,50±0,23	0,097

Table 2: Oxidant state parameters (Mean±SEM).

	Group C (n=6)	Group DC (n=6)	Group DIR (n=6)	Group DIRS (n=6)	Group DIRD (n=6)	P**
GST (mIU/mg.protein)	1,29±0,11	10,09±0,71*	12,55±2,34*	8,24±0,53*,&	6,96±1,42*,&	<0,0001
CAT (IU/mg.protein)	5439,40±1436,19	11661,60±1368,07	19054,83±3311,60*,?	9253,50±1301,51 &	10120,33±2068,71 &	0,003
NOS (IU/mg.protein)	89,82±34,53	162,72±31,54	408,90±129,07*,?	172,75±55,00&	152,22±50,67&	0,043
TBARS (nmol/mg.protein)	11,15±1,91	23,61±2,71*	34,72±3,05*,?	21,61±2,89*, &	19,04±0,98*, &	<0,0001
SOD (U/mg protein)	78,85±27,34	209,60±28,03	493,78±122,96*,?	111,75±11,50&	145,70±37,98&	<0,0001

P**: Kruskal-Wallis test - Significance level p<0.05, *p<0.05: Compared to group C; &p<0.05: Compared to group DIR; ?p<0.05: Compared to group DC.

Malondialdehyde is measured as TBARS. Although MDA is not specific, it correlates well with the degree of lipid peroxidation. Several studies have been published showing the beneficial effects of different agents on the kidney in IRI. Ascorbic acid acts via free radical scavenging systems and shows antioxidant activities (32), and iloprost inhibits lipid peroxidation (33). Leptin increases nitrite and decreasing tumor necrosis factor-alpha (TNF-α) levels (34). The antioxidant effect of levosimendan is owing to the NO-related mechanisms (35). Doxycycline decreases the level of proinflammatory cytokines (36).

Volatile anesthetics, one of the main components of general anesthesia, also have significant effects, such as immune system modulation (37-39). It is thought that trifluoro carbon in molecular structures is responsible for the immune-modulatory effect, and lipid solubility is related to renal protection (40). They have a protective effect in renal tubules through externalization of membrane phosphatidylserine and the release of transforming growth factor (TGF)-β1 in the proximal renal tubule (41).

In experimental studies published in recent years, desflurane preconditioning has been shown to protect the kidney against IRI by regulating the pathway of Nrf2-Keap1-ARE signal, inhibiting oxidative stress, and inflammation (42)]. Sevoflurane has been reported to exert a protective effect against kidney damage by

reducing the expression of TNF-α and NF-κB in renal IRI (43). It demonstrated that upregulation of HIF-2α through sevoflurane pretreatment could improve the renal dysfunction caused by IRI (44).

A randomized clinical study performed on renal transplantation showed that renal protective effects of sevoflurane and desflurane were demonstrated by similar preoperative and postoperative serum creatinine, Interleukin (IL)-2, and TNF-α levels (45).

In our study, SOD, CAT, GST, NOS enzyme activities, and TBARS levels as IRI biochemical markers significantly increased in diabetic rats compared to the control group. SOD, CAT, and GST enzyme activities and TBARS levels were lower in the sevoflurane and desflurane groups than the DIR group without medication.

As histopathological markers, VVH, GV, THC, LI, BSD, TD, and THDN levels were significantly increased in the DIR group. On the other hand, these parameters were significantly decreased in the desflurane group compared to the sevoflurane group, while the BSD was significantly increased in the desflurane group. All these data were interpreted as that sevoflurane and desflurane reduced the effects of lower extremity IRI on the kidney, created by clamping the abdominal aorta.

5. Conclusions

These biochemical and histopathological findings indicate partial renoprotective effects of sevoflurane and desflurane at the second hour of reperfusion. More clinical and experimental studies are needed to prevent and treat IRI-induced AKI effectively.

Conflict of Interests

The authors declare that there is no conflict of interest.

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None

Author Contributions

Aydin ME and Arslan M contributed to the conception and design of the study. Sezen CS contributed to the collection of the data and statistical analysis and evaluation of the results. Bayraktar AC contributed to the creating and writing of the manuscript. Erbatur ME and Kavutcu M contributed to revising the work and final approval of the version.

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