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Comparison of the protective effects of desflurane and propofol anesthesia in rats: a hepatic ischemia-reperfusion injury model

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Aim: It is known that desflurane and propofol protect liver tissue via different mechanisms. The aim of this study was to compare the protective effects of these 2 agents against hepatic ischemia-reperfusion injury.

Materials and methods: Rats were randomly divided into 2 groups: ischemia and ischemia-reperfusion. Each group was further divided into 3 subgroups: ketamine, desflurane, and propofol. Thirty minutes after anesthetics were administered, the rats were subjected to 45 min of hepatic ischemia and 4 h of reperfusion. Blood samples and liver tissues were obtained in order to assess serum tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and malondialdehyde levels and for histologic examination.

Results: The postischemic serum IL-1β levels were significantly higher with propofol than with ketamine ($P = 0.014$). In the postischemic period, in the ischemia-desflurane group, TNF-α levels were significantly lower than in the ischemia-propofol ($P = 0.009$). The number of polymorphonuclear leukocytes was the lowest in the ketamine group in the postischemic period ($P < 0.01$).

Conclusion: In order to reach a definitive judgment, studies with a larger number of subjects are necessary.

Key words: Liver, ischemia-reperfusion injury, desflurane, propofol

1. Introduction

The interruption of hepatic inflow is a common procedure conducted during liver transplantation, resectional surgery, and trauma surgery (1). However, after a period of hepatic ischemia, blood flow and oxygen supply are reestablished; reperfusion enhances the injury caused by ischemia. This phenomenon, known as ischemia-reperfusion (IR) injury, directly affects liver viability (2).

Reperfusion after ischemic injury triggers the activation of several transcription factors, including nuclear factor (NF)-κB, which in turn alters the transcription of multiple genes associated with the inflammatory response, including intracellular adhesion molecule-1, interleukin (IL)-1β, IL-8, and tumor necrosis factor (TNF)-α. The release of reactive oxygen species from activated Kupffer cells leads to the generation of end products of lipid peroxidation, such as malondialdehyde (MDA) (3,4).

Desflurane and propofol are frequently used in general anesthesia. Previous studies have shown that both of these drugs protect against IR injury of the liver via different mechanisms (5–8).

We designed the present study to determine which of the 2 drugs has a greater effect on the changes in systemic cytokine levels (IL-1β and TNF-α), MDA levels, and liver histopathology in a rat model of hepatic IR.

2. Materials and methods

All experimental protocols were approved by the Animal Research Committee at Gazi University, Ankara, Turkey. All animals were maintained in accordance with the recommendations of the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

Thirty adult male Wistar rats weighing 250–330 g each were maintained on a 12-h night/day cycle and allowed free access to food and water at all times until the experiments. All rats were anesthetized with 50 mg/kg intramuscular (IM) ketamine (Ketalar®; 1 mL = 50 mg; Pfizer, İstanbul, Turkey) and 0.01 mg atropine (Atropin Sülfat®; 0.5 mg/mL; Biofarma, İstanbul, Turkey). They were placed on an electric heating pad under a warming light, and the body temperatures were continuously monitored using a rectal

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thermometer. Their temperature was maintained at 37 °C. After tracheal intubation with a 16-gauge (G) intravenous (IV) cannula, the animals' lungs were artificially ventilated with a rodent model ventilator (Inspira ASV; Harvard Apparatus, Hollistone, MA, USA). The ventilatory rate was set at 80 strokes/min with a tidal volume of 10 mL/kg. The tail vein was cannulated with a 24-G IV cannula for drug administration and hydration. After a local anesthetic effect was achieved using 1% lidocaine HCl (Jetmonal®; 2%; Adeka, Samsun, Turkey), a midline abdominal incision was performed. The abdominal aorta was identified, and a 26-G IV cannula (Ar-Es IV Neo, İzmir, Turkey) was inserted to enable direct measurement of the mean arterial blood pressure (MABP), heart rate (HR), and blood gas analysis.

The rats were randomly divided into 2 groups: ischemia (I) and ischemia-reperfusion (IR). Each group was further divided into 3 subgroups of 5 rats each: a ketamine group (Group I-K and Group IR-K), receiving intramuscular 50 mg/kg ketamine injections every 30 min; a desflurane group (Suprane®; 240 mL; Baxter, İstanbul, Turkey) (Group I-D and Group IR-D), in which 6% desflurane was administered with oxygen via anesthesia apparatus; and a propofol group (Propofol®; 1%; Fresenius Kabi AB, Leipzig, Germany) (Group I-P and Group IR-P), receiving hourly 20 mg/kg IV infusion via a pump (Eczacıbaşı Baxter Healthcare volumetric infusion pump; İstanbul, Turkey). No muscle relaxants were given to the animals to ensure that the depth of general anesthesia was observable. Thirty minutes after the administration of the anesthetic drugs, the liver was exposed and the ligamentous attachments of the left lateral and median lobes were carefully divided. The left lateral and median lobes were freed. The portal circulation of these lobes was dissected, and the portal vein and the hepatic artery supplying the median and left lateral lobes were blocked with an atraumatic vascular clamp (Harvard Apparatus). Intestinal venous congestion was prevented by retaining portal and arterial inflow with venous outflow in caudate and right lateral lobes. This procedure resulted in the induction of ischemia in approximately 65%–70% of the liver. After 45 min of ischemia, the clamp was removed. The rats in Groups I-K, I-D, and I-P were sacrificed by hemorrhage at the end of the ischemic period. The rats in Groups IR-K, IR-D, and IR-P were subjected to hepatic ischemia followed by reperfusion for 4 h, and were also sacrificed at the end of the reperfusion period. Blood samples were withdrawn and were centrifuged at 3000 rpm for 5 min (Centronic-BL; JP Selecta, Barcelona, Spain). Following the collection of supernatant liquid, the samples were stored at –80 °C until assayed for the measurement of TNF-α, IL-1β, and MDA. Additionally, liver samples from the left lateral and median hepatic lobes were collected and fixed with 10% formalin and embedded in paraffin for histologic examination.

Serum TNF-α and IL-1β levels were determined in a 96-well microplate, using a commercial enzyme-linked immunosorbent assay kit (BioSource International, Inc., Camarillo, CA, USA) according to the manufacturer's guidelines. All samples were tested in duplicate. The plate was read on an ELx800 automated microplate reader (Bio-Tek Instruments, Inc., Winooski, VT, USA) at 450 nm. The concentrations of TNF-α and IL-1β were compared with the standard curve and expressed as pg/mL. The minimal detectable protein concentration was 8–16 pg/mL.

MDA concentration, a product of lipid peroxidation, was also measured. Tissue samples from the liver were homogenized with a Virsonic 100 (Virtis Company Inc., Gardiner, NY, USA) ultrasonic homogenizer. Briefly, 0.1 mL of homogenate was mixed with 0.1 mL of 8.1% sodium dodecyl sulfate, 0.75%; 0.8% thiobarbituric acid; and 0.3 mL of distilled water and kept in a boiling water bath for 60 min. After cooling, 0.5 mL of distilled water and 2.5 mL of 15:1 (v/v) n-butanol/pyridine were added. After centrifugation at 4000 rpm, the absorbance of the supernatant at 532 nm was measured with spectrophotometry (Shimadzu Corp., Tokyo, Japan) against a calibration curve obtained from a MDA standard. The results were expressed as nmol/L protein.

For morphological assessment of hepatic injury and polymorphonuclear leukocytes (PNLs), adhesions were performed by a pathologist blinded to tissue sections prepared at 6-μm intervals and stained with hematoxylin-eosin. Sections were evaluated at 200× magnification for severity of injury and graded using an ordinal scale as follows: grade 0, minimal or no evidence of injury; grade 1, mild injury consisting of cytoplasmic vacuolation and focal nuclear pyknosis; grade 2, moderate to severe injury with extensive nuclear pyknosis, cytoplasmic hypereosinophilia, and loss of intercellular borders; and grade 3, severe necrosis with disintegration of hepatic cords, hemorrhage, and PNL infiltration.

2.1. Statistical analysis

All data were expressed as mean ± standard deviation (SD). Comparisons between multiple groups were performed using the Kruskal–Wallis test. When a difference was detected, specific differences were identified using the Bonferroni corrected Mann–Whitney U test. SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to complete all the analyses, and $P < 0.05$ was considered statistically significant.

3. Results

Throughout the experiment, the HR ranged between 115 and 324 bpm for all groups. The MABP levels were comparable among the groups. There were no significant

differences in HR among the groups; however, the HR levels of Group IR-D in the fifth minute of the ischemic period were lower than those of Group IR-K (P = 0.009) (Table 1). Additionally, pH levels and $PaCO_2$ tensions were comparable, and no significant differences were found within the groups.

In order to determine whether serum cytokine levels correlated with tissue injury, IL-1β and TNF-α levels were measured. As shown in Figure 1, the highest levels of IL-1β were found in Group I-P among ischemia groups. The levels of IL-1β in Group I-P were significantly higher than those of Group I-K (P = 0.014). Postreperfusion measurements showed an increase with all 3 agents of the groups. While the highest levels of IL-1β were observed in Group I-P at the end of I, the lowest level was recorded for Group IR-P at the end of R.

The serum TNF-α findings for all groups are shown in Figure 2. The TNF-α levels of Group I-D were significantly lower than those of Group I-P (P = 0.009). Although there were no significant differences in postreperfusion measurements, the lowest TNF-α levels were found in Group IR-D.

The liver contents of lipid peroxidation by-product MDA levels can be seen in Figure 3. Although the maximum values of tissue MDA levels were found in Group IR-P, and the lowest values in Group IR-K, there were no significant differences in liver MDA contents among any of the 3 groups (P > 0.05).

Liver biopsy specimens were obtained after ischemia and 4 h of reperfusion (Figure 4). The assessment of the liver sections from Group I-D showed Grade 1 (80%) or 2 (20%) hepatic injury, which was the same as in Group I-P. However, postreperfusion liver slices showed more severe Grade 2 injury for both desflurane (40%) and propofol (60%) administration than postischemic slices. However, this worsening of the hepatic injury was statistically insignificant (P = 0.262). None of the groups had a Grade 3 hepatic injury (Table 2).

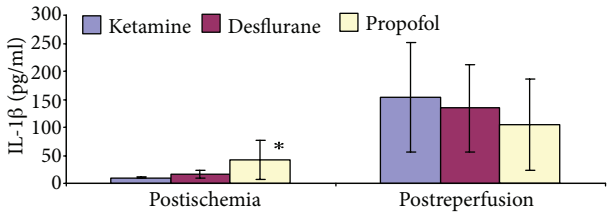

Figure 1. Serum IL-1β concentrations in rats postischemia and postreperfusion. Each bar represents the mean ± SD. *: P < 0.05 versus Group I-K.

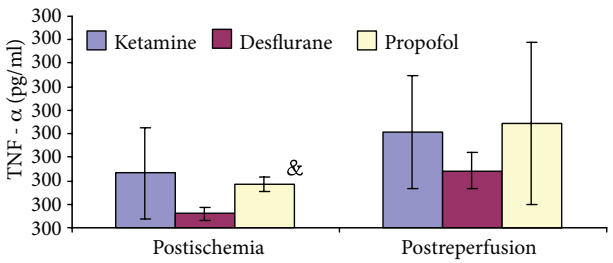

Figure 2. Serum TNF-α concentrations in rats postischemia and postreperfusion. Each bar represents the mean ± SD. &: P < 0.01 versus Group I-D.

Table 1. Time course of changes in HR in experimental groups.

		Group I-K (n = 5)	Group I-D (n = 5)	Group I-P (n = 5)	Group IR-K (n = 5)	Group IR-D (n = 5)	Group IR-P (n = 5)
Preischemia	30	252.40 ± 42.26	207.60 ± 46.16	208.20 ± 32.93	250.20 ± 42.07	189.20 ± 24.92	235.40 ± 49.60
	15	242.80 ± 36.64	192.20 ± 36.96	224.00 ± 25.19	252.60 ± 46.74	194.00 ± 23.92	222.40 ± 43.90
Ischemia	0	245.40 ± 57.84	199.40 ± 48.13	210.80 ± 15.32	256.00 ± 49.18	182.80 ± 23.12	217.00 ± 58.08
	5	268.80 ± 45.92	186.80 ± 44.74	216.00 ± 44.06	265.00 ± 35.16	179.40 ± 25.56*	212.60 ± 63.83
	15	250.40 ± 48.09	192.60 ± 43.51	208.00 ± 35.41	264.80 ± 30.25	194.00 ± 16.00	221.80 ± 76.38
	45	242.60 ± 52.13	183.20 ± 54.66	195.80 ± 34.38	244.00 ± 34.54	193.00 ± 21.59	201.00 ± 44.64
Reperfusion	5				225.40 ± 24.79	189.40 ± 34.72	205.20 ± 52.19
	15				230.20 ± 39.88	185.20 ± 36.22	197.80 ± 50.85
	30				220.00 ± 56.09	182.00 ± 38.81	182.40 ± 48.34
	60				205.40 ± 60.11	183.40 ± 38.70	162.80 ± 33.49

Data are expressed as mean ± SD. *: P < 0.05 vs. Group IR-K.

Table 2. Histopathologic liver changes.

	Severity of hepatic injury			
	G_0 (n)	G_1 (n)	G_2 (n)	G_3 (n)
Postischemia				
Ketamine	1	4		
Desflurane		4	1	
Propofol		4	1	
Postreperfusion				
Ketamine	1	3	1	
Desflurane		3	2	
Propofol		2	3	

G: grade. See text for further details.

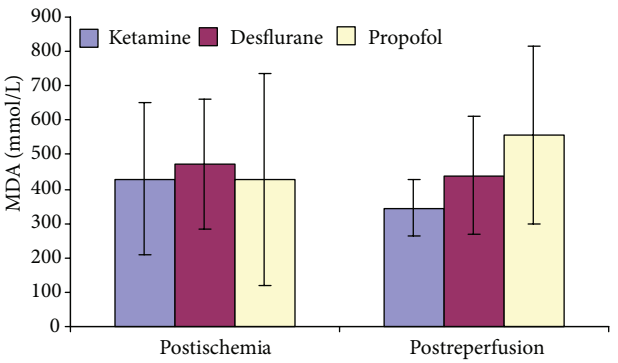

Figure 3. MDA levels in liver. Each bar represents the mean ± SD. There was no statistical significance among the groups.

As seen in Table 3, the number of PNLs was the lowest in Group I-K ($P < 0.01$). Although there was an increase in PNLs after the R period in all 3 groups, it was not statistically significant ($P > 0.05$).

4. Discussion

In our study, we compared the protective effects of desflurane and propofol using a hepatic ischemia-reperfusion model in rats. We concluded that the protective effects of desflurane are stronger because its effect acts through TNF-α, which was detected at lower levels both at the end of ischemia and reperfusion.

Tumor necrosis factor-α, IL-1β, and MDA levels were used to evaluate IR injury in various tissues in both clinical and experimental studies (1,6–15). During hepatic ischemia, the increase in TNF-α levels remains detectable, both in the plasma and liver tissue, until the late phase of reperfusion (10). In a study using rats, with a partial hepatic ischemia model, following IR, a significant increase in the plasma TNF-α and macrophage inflammatory protein-2 levels was reported (11,12). Similarly, we also observed a significant increase in the plasma TNF-α and IL-1 levels after reperfusion.

In animal experiments, increasing TNF-α levels caused both hepatic and pulmonary damage (13). Thus, TNF-α not only acts locally but also systemically, resulting in functional impairment in other organ systems. Studies on liver allograft rejections strongly suggested that TNF-α and IL-1 play a role in the early phase of rejection and that the specific inhibition of cytokines can prevent allograft rejection (14).

A study with a rat hepatic IR model indicated that TNF-α antibody had a protective effect against IR, and alanine aminotransferase (ALT) and MDA levels decreased significantly compared to the control group, in which no TNF-α antibody was administered (15). In other studies with similar models, the IL-1 receptor blockade was shown to decrease tissue damage and thus decrease mortality (16,17). This evidence suggests that the anesthetic agent that greatly prevents the increase in TNF-α, IL-1, and MDA levels will have the best protective effects against tissue damage.

Desflurane is almost immune to biological degradation, with a 0.02% calculated metabolism ratio, and is less soluble in plasma and tissues. Thus, it has almost no risk of hepatotoxicity (5) and is preferred in hepatobiliary surgery as it has a protective effect on the hepatic blood flow and causes less toxicity (18). Furthermore, pretreatment with desflurane limits the NF-κB activation, which is stimulated by TNF-α, leading to a cellular protective effect (6). The extent of myocardial infarct was reported to decrease in dogs with cardiac IR that were pretreated with desflurane (19). In a similar study in human umbilical vein cells, the expression of the adhesion molecules, stimulated by TNF-α, and the prevention of neutrophil adhesion was reported (20). In our study, when desflurane was used, TNF-α levels were lowest at the end of the reperfusion.

Table 3. Count of PNLs.

	Group I-K (n = 5)	Group I-D (n = 5)	Group I-P (n = 5)	Group IR-K (n = 5)	Group IR-D (n = 5)	Group IR-P (n = 5)
PNL	6.00 ± 1.58	13.80 ± 4.76	12.40 ± 5.41	14.00 ± 9.82	15.80 ± 5.98	19.80 ± 6.80

Data are expressed as mean ± SD.

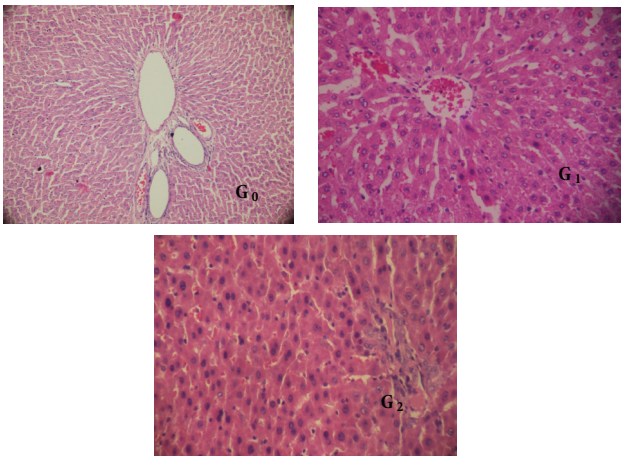

Figure 4. Hepatic histopathology following IR. G_0: Normal hepatic histology. G_1: Vacuolar degeneration and low counts of apoptotic cells. G_2: Loss of cytoplasmic membrane, diffuse eosinophilia with many apoptotic cells. The liver sections were prepared and stained with hematoxylin and eosin, 400×.

However, we did not observe a comparable decrease in IL-1 levels.

Propofol is an intravenous anesthetic agent. Its 2,6-diisopropylphenol component is chemically similar to other radical scavengers, such as butylene hydroxytoluene, from the phenol hydroxyl group, and vitamin E. This suggests that propofol also has a radical-scavenging property (21).

In both in vivo and in vitro studies, propofol has been reported to have a protective effect against lipid peroxidation in many tissues (22–24). In addition, studies with rat tissue cultures indicate that propofol protects the liver tissue from peroxidation (25,26). It inhibits inducible nitric oxide synthase over-expression, which activates its antiinflammatory effects in the liver (27). According to recent studies, propofol has antioxidant and antiinflammatory properties (28,29). Contrary to these studies supporting its antioxidant properties, an in vitro study of rat liver tissue samples showed that propofol has no protective effects against IR damage. This is possibly because propofol and its lipid contents cannot be metabolized in the damaged liver tissue, which results in the accumulation of propofol (30). In our study, after propofol administration, end-reperfusion TNF-α levels were higher than those of both desflurane and ketamine. This suggests a stronger cytokine response after propofol administration, and a lack of hepatoprotective effect.

In a study similar to ours, which compared the effect of desflurane and propofol-remifentanil (TIVA) on postoperative renal and hepatic functions after right hepatectomy in living donors, aspartate aminotransferase and ALT levels increased in both groups, while total bilirubin levels and the international normalized ratio, which are associated with liver damage, were higher in the TIVA group. Furthermore, in the TIVA group, creatinine levels were high and the glomerular filtration rate was low. In light of these results, desflurane is proposed as the best choice during liver transplantation (18).

In conclusion, no significant differences were found between the 2 agents in terms of the IL-1β and MDA levels and histopathological examination. A difference was only observed in the TNF-α levels, but this was attributed to the small number of subjects. In order to reach a conclusion, further studies should be conducted with a larger number of subjects. In addition, in surgical interventions of long duration, such as liver transplantation, propofol causes an excessive lipid load. For this reason, we think that desflurane use can be more advantageous in this type of surgery.

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