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The Effect of Desloratadine Upon Ischemia-reperfusion-induced Oxidative and Inflammatory Gastric Injury in Rats

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ABSTRACT

Background: Ischemia-reperfusion (I/R) injury is a pathological process mediated by oxidative stress and inflammation that begins with oxygen deprivation. This study, it was aimed to investigate the protective effect of desloratadine on gastric I/R damage in rats. **Methods:** Eighteen rats were randomly divided into 3 groups gastric I/R (GIR), gastric I/R + 5 mg/kg oral desloratadine (GIRD) and gastric sham operation (GSG). One hour later desloratadine administration, clips were placed in the celiac arteries of the rats in the GIRD and GIR groups. Ischemia was created by keeping the clips closed for one hour. Afterward, the clips were removed and reperfusion was achieved for three hours. The sham operation was performed on the GSG group. Then, all animals were euthanized with 120 mg/kg ketamine. Malondialdehyde (MDA), total glutathione (tGSH), superoxide dismutase (SOD) catalase (CAT) and interleukin-6 (IL-6) levels were determined in the excised gastric tissues. All tissues were also analyzed histopathologically. **Result:** When the GIR group was compared with the GSG, an increase in MDA and IL-6 levels and a decrease in tGSH, SOD and CAT levels were observed (p<0.001). In addition, severe mucosal degeneration, congestion, polymorphonuclear leukocyte infiltration and mucosal edema were detected in the GIR group. Desloratine significantly inhibited both biochemical and histopathological changes (p<0.05).

Keywords: Desloratadine, Gastric injury, İschemia-reperfusion, Oxidative stress, Rats.

INTRODUCTION

Ischemia is the deoxygenation of the tissue due to the reduction of blood reaching the tissues, while reperfusion is the reoxygenation (O_2) of the tissue by restoring the blood flow (Yapca *et al*., 2013). Ischemia is encountered in a wide variety of pathologies such as myocardial infarction, stroke, trauma and circulatory arrest. Reperfusion procedure essential to be performed in these cases causes serious complications (Eltzschig and Eckle, 2011). Gastric ischemia-reperfusion (I/R) is a remarkable condition that develops in more than 80% of patients undergoing surgical procedures (Pena-Mercado *et al*., 2016). I/R injury begins with the accumulation of hypoxanthine) and xanthine oxidase in the tissue during the ischemia period. O_2, which is abundantly supplied to the ischemia tissue in reperfusion, initiates the metabolism of hypoxanthine with xanthine oxidase and induces the formation of reactive oxygen species (ROS) (Yapca *et al*., 2013). ROSs are highly reactive due to having unpaired electrons (Yamasaki, 2023). Therefore, ROSs cause oxidation (LPO) of cell membrane lipids, resulting in the formation of oxidant products such as malondialdehyde (MDA) from lipids (Gundogdu *et al*., 2022). Moreover, ROS stimulates the formation of proinflammatory cytokines and increases the level of damage (Minutoli *et al*., 2016). Therefore, I/R injury is defined as a pathological process triggered by the decrease in oxygen reaching the tissue, developing ROS production and inflammatory events (Yapca *et al*., 2013).

Desloratadine, whose protective effect on gastric I/R-related damage was investigated in this study, is a non-sedating H_1 receptor antagonist drug (Henz, 2001; Kocaturk *et al*., 2020). Kocaturk *et al*. reported that desloratadine protects kidney tissue from I/R injury inhibiting the increase in MDA and decrease in total glutathione (tGSH) (Kocaturk *et al*., 2020). Kadioglu *et al*. revealed that desloratadine protects ovarian tissue from inflammatory I/R injury suppressing the increase of proinflammatory cytokines responsible for inflammation such as nuclear factor-κB (NF-κB), tumor necrosis factor-alpha (TNF-α) and interleukin 1 beta (IL-1β) (Kadıoğlu *et al*., 2020). This information suggests that desloratadine may be beneficial in preventing

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gastric I/R injury. In the literature, there have been no studies how desloratadine affected the damage caused by I/R in the stomach. Therefore, in this study was aimed to determine the effect of desloratadine on experimentally induced gastric I/R injury in rats by biochemical and histopathological examination.

MATERIALS AND METHODS

Animals

Eighteen Albino *Wistar* male rats (255-268 g) were included in this study. The animals were procured from Erzincan Binali Yildirim University Experimental Animals Application and Research Center (Erzincan, Turkey). Experimental applications were carried out in the same center in October 2022. The rats were housed in an environment with adjusted temperature (22°C) and light (12 h light/dark). During this time, the rats were given standard chow and tap water ad lib. Experimental procedures were approved by the Local Animal Experimentation Ethics Committee (Meeting date: 29.09.2022, decision no: 09/45). Experiments were carried out in Erzincan Binali Yildirim University Experimental Animals Application and Research Center laboratories in November 2022.

Chemical substances

Desloratadine was obtained from Sanofi (Turkey), ketamine from Pfizer (Turkey) and sevoflurane from Kocak Farma (Turkey).

Experimental groups

The animals were categorized under 3 groups as gastric I/R treatment (GIR), gastric I/R treatment+5 mg/kg desloratadine (GIRD) and gastric sham operation (GSG).

Anesthesia procedure

Ketamine [60 mg/kg, intraperitoneal (i.p)] and sevoflurane (inhaler) were used for anesthesia. For the surgical intervention, the animals were expected to remain motionless in the supine position (Demiryilmaz *et al*., 2014).

Experimental procedure

Desloratadine 5 mg/kg (Kocaturk *et al*. 2020) was given orally by gavage to the GIRD (n=6) group of animals. Distilled water was applied to the stomach with the same method to GIR (n=6) and GSG (n=6) groups. One hour after administrating desloratadine and distilled water, all animal groups were anesthetized as mentioned above. During the anesthesia period, laparotomy was performed on the rats with a 2.5 cm long midline incision and reached to the stomach. Subsequently, the clip was placed in the celiac artery of the GIRD and GIR animal groups. Ischemia was created by keeping the clips closed for one hour. Then, the clips were removed and the incisions were sutured and reperfusion of the stomach tissue was provided for three hours. The celiac artery of the GSG group was not clipped and the opened abdomen was closed by suturing (Wada *et al*., 1996). Immediately after three-hour reperfusion procedure, all animals were euthanized with 120 mg/kg ketamine (i.p) and gastric tissues were removed. Then, the levels of MDA, tGSH, superoxide dismutase (SOD), catalase (CAT) and interleukin 6 (IL-6) in the stomach tissues were measured. In addition, the tissues were examined histopathologically.

Biochemical analysis

MDA, GSH, SOD, CAT and protein determination

MDA, GSH and SOD determination in tissue samples was measured with commercial animal enzyme-linked immunosorbent assay (ELISA) kits and each assay was performed according to kit instructions (item no 706002, 703002 and 10009055, respectively, Cayman Chemical Company). CAT determination was performed according to the method suggested by Goth (1991). Protein determination was analyzed spectrophotometrically at 595 nm according to the Bradford method (Bradford, 1976).

IL-6 analysis

Tissue samples were weighed and cut. It was then frozen in liquid nitrogen and homogenized with a pestle and pestle. After the samples were thawed, they were stored at 2-8°C. PBS (pH 7.4, 1/10 (w/v)) was added, then, the vortex was kept for 10 seconds, centrifuged for 20 minutes at 10000 xg and the supernatants were collected. The levels of IL-6 were measured using a commercial kit procured from Eastbiopharm Co. Ltd. ELISA kit, China.

Histopathological analysis

The tissues were fixed in 10% formaldehyde solution for 72 hours. Tissues were then cassetted, washed in running water for 24 hours and then dehydrated by passing through 70%, 80%, 90% and 100% alcohol, respectively. The stomach tissues cleared in xylol were embedded in paraffin blocks and 4-5 thick micron sections were taken. The sections were stained with hematoxylin-eosin and analyzed and photographed in the Olympus DP2-SAL firmware software (Olympus® Inc. Tokyo, Japan). Serial sections were scored under the criteria of mucosal degeneration, necrotized cells, dilatation/congestion, polymorphonuclear cell (PMNL) infiltration and mucosal edema. For the listed criteria, scoring was made between 0-3 points as 0:no injury, 1:mild injury, 2:oderate injury and 3:severe injury.

Statistical analyses

Analysis of biochemical data was done by ANOVA. Tukey HSD was subsequently performed. Results were presented as “mean value ± standard deviation” (X±SD). Since the histopathological grading data were semi-quantitative, the Kruskal-Wallis test was used. Dunn’s test was subsequently performed. Histopathological data were expressed as median (minimum-maximum). All statistical processes were performed with “SPSS for Windows, 22” statistical software and $p<0.05$ value was considered significant. GraphPad 9 program was used for graphics.

RESULTS AND DISCUSSION

Gastric injury induced by I/R is a possible clinical problem to appear in many conditions such as peptic ulcer bleeding, hemorrhagic shock and surgery (Kuyrukluyildiz *et al*., 2021). In the literature, I/R injury has been defined as a pathological event that begins with ischemia, continues with oxidative stress and expands with inflammation (Kocaturk *et al*., 2020). In this study, the protective effect of desloratadine against possible gastric injury induced by I/R was analyzed biochemically and histopathologically.

As known, I/R causes oxidative stress with the increase in ROS production (Ding *et al*., 2021). ROSs oxidizes cell membrane lipids, causing an increase in toxic oxidant products such as MDA (Xuying *et al*., 2022). As seen in Table 1, MDA levels in gastric tissues of the animals in GIR group underwent gastric I/R were found higher than in sham group (p<0.001). Similarly, Omayone *et al*. found that MDA levels increased in gastric tissue applied I/R (Omayone *et al*., 2020).

This study analyzed non-enzymatic and enzymatic antioxidant levels such as tGSH, SOD and CAT besides oxidant parameter measurement. Cellular protection against the oxidation of ROS was mainly provided by GSH, SOD and CAT (Poljsak *et al*., 2013; Ravikumar *et al*., 2022). In the literature, there was information about GSH having various physiological functions including ROS scavenging and electrophile elimination (Liu *et al*., 2022). Kuyrukluyildiz *et al*. (2021) determined that I/R procedure decreased tGSH levels in the stomach tissue. In this study, in group comparisons performed in terms of tGSH levels, the values in GIR group were determined lower than the healthy animals (p<0.001, Table 1). SOD as an enzymatic antioxidant analyzed in this study was considered to be the first defense line that eliminated the superoxide radical (O2") formed in the body (Cui *et al*., 2013). It was stated by Cui *et al*. that the decrease in SOD levels due to gastric I/R was induced by the depletion of antioxidant capacity due to oxidative stress (Cui *et al*., 2013). Supporting this information, our biochemical results determined that SOD levels were lower in the I/R group than in the GSG group (p<0.001, Table 1). Another parameter measured in gastric tissue was CAT. It is known that CAT has been known to be an enzyme that decomposed hydrogen peroxide into molecular oxygen and water (He *et al*., 2017). In our study, the CAT level was found to be lower in the I/R group with high MDA and low tGSH and SOD levels compared to healthy animals (p<0.001, Table 1). Similarly, Odukanmi *et al*. found that CAT levels were decreased due to I/R-induced damage in the stomach (Odukanmi *et al*., 2018). Literature information and our experimental results suggested that exposure of the stomach to I/R caused oxidative stress, the oxidants increased and antioxidant levels decreased after depletion.

It was understood from the literature that inflammatory events also played roles in I/R injury (Kocaturk *et al*., 2020). Therefore, IL-6 levels were determined to analyze the inflammatory activity in this study. Our biochemical results revealed that IL-6 levels in the GIR group were increased compared to the healthy group (p<0.001, Table 1). The increase in IL-6 levels occurs in cases such as oxidative tissue damage due to increased ROS. Because induced oxidative stress activates the transcription factor of NF-κB, which regulated IL-6 expression and this results in more IL-6 production (Kumari *et al*., 2016). On the other hand, IL-6 expression also causes an increase in ROS production (Han *et al*., 2021). Magierowska *et al*. also revealed that gastric I/R in rats increased IL-6 (Magierowska *et al*., 2019).

I/R injury on the gastric tissue was also analyzed histopathologically. As seen in Fig 1A and Table 2, tunica mucosa surface epithelium and glands, gastric stratification and wall structure were considered normal in gastric tissues of animals in the GSG group. In the sections belonging to the GIR group, the surface epithelium was monitored to be partially ruptured and shed; and necrotized cell groups were observed under the spilled surface epithelium. Moreover, it was observed that the gland recesses decreased, the neck regions of the glands were opened, the base regions were severely edematous and the blood capillaries had intense dilation and congestion. Severe PMNL infiltration was also noted in the connective tissue area around the vessel and adjacent to the gland bases in the samples belonging to this group (Fig 1B and Table 2). It was stated in the literature that I/R-induced ROS increase played a role in the formation

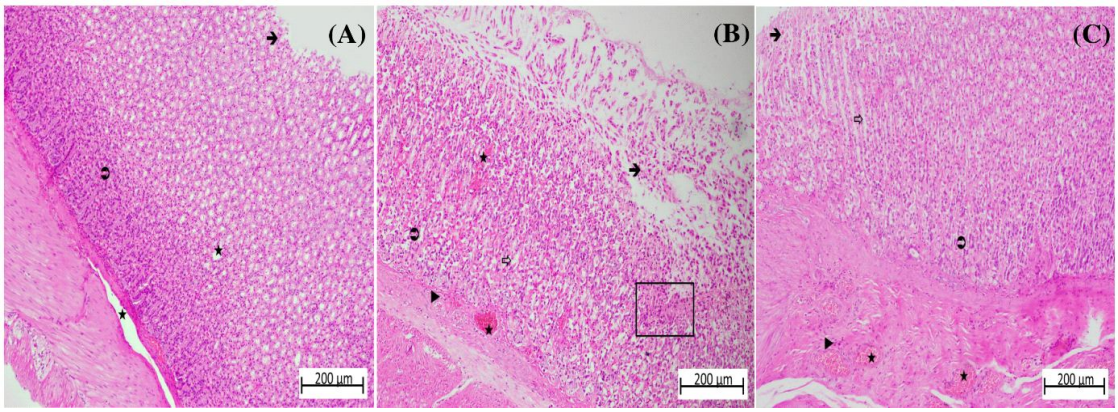
Table 1: Analysis results of biochemical parameters in stomach tissues of animal groups.

Variables	GSG	GIR	GIRD	F/p
	X ±SD (mean±standard deviation)			
MDA (µmol/mg protein)	4.14±0.08a	7.23±0.07b	4.56±0.21c	909.762/0.001
tGSH (nmol/mg protein)	7.27±0.12a	4.20±0.27b	6.83±0.25c	405.290/0.001
SOD (U/mg protein)	8.33±0.25a	5.33±0.27b	7.54±0.26c	215.449/0.001
CAT (U/mg protein)	6.81±0.11a	3.84±0.09b	6.19±0.13c	1220.789/0.001
IL-6 (ng/L)	3.12±0.07a	6.07±0.35b	3.77±0.13c	304.648/0.001

abc: p<0.05, different letters on the same line show significant difference between groups. MDA: Malondialdehyde; tGSH: Total glutathione; SOD: Superoxide dismutase; CAT: Catalase; IL-6: Interleukin 6; GSG: Sham operation group; GIR: Ischemia-reperfusion group; GIRD: Ischemia-reperfusion+5 mg/kg desloratadine group. Statistical analysis was done with one-way ANOVA, post hoc Tukey HSD test was used.

of acute gastric mucosal lesions (Wada *et al*., 1996). It was reported in a previous study that the I/R procedure increased gastric surface epithelial damage, edema, dilatation of capillaries, congestion and PMNL infiltration (Kuyrukluyildiz *et al*., 2021). Similarly, Omayone *et al*. (2020) reported that I/R induced gastric necrosis and inflammatory cell infiltration in the submucosa.

Desloratadine was a selective H_1 receptor blocker and a non-sedating antihistaminic drug analyzed in terms of its protective effect upon oxidative gastric injury due to gastric I/R. Previous studies suggested that desloratadine not only had an antihistamine but also had an antioxidative effect (Tatar *et al*., 2015). Furthermore, in the literature, there was information that desloratadine cleared O2- and caused a decrease in ROS levels in patients with chronic idiopathic urticaria (Sadowska-Woda *et al*., 2010b). In the literature review, no study was found investigating the effect of desloratadine on gastric I/R. However, the effect of desloratadine upon increased oxidative stress with kidney I/R was investigated by Kocaturk *et al*. (2020) and it was suggested to prevent the increase of MDA. Similarly, our study also indicated that desloratadine suppressed the increase of MDA significantly compared to the animals in the I/R group (p<0.001, Table 1). In addition, our analysis results showed that desloratadine inhibited the decrease of tGSH, SOD and CAT levels with I/R (p<0.01, Table 1).Tatar *et al*. (2015). reported that desloratadine prevented the decrease of GSH and SOD levels in the allergic rhinitis model. Cassano *et al*. (2006) also reported that desloratadine efficiently protected the SOD level against the harmfull effects of oxidative stress. It was found in a study carried out on children that desloratadine treatment



A: Hematoxylin- eosin staining in the stomach tissue of the GSG group; ➔: surface epithelium, ➲: gastric glands, ★: blood vessel, x100. **B:** Hematoxylin- eosin staining in gastric tissue belonging to GIR group; ➔: shed and degenerated surface epithelium, ☐: necrotized cell groups, ➲: edematous gastric glands, ⇨: severe edema of the mucosa, ▶: severe polymorphonuclear cell infiltration, ★: severe dilated and congested blood vessel, x100. **C:** Hematoxylin - eosin staining in gastric tissue belonging to the GIRD group; ➔: normal surface epithelium, ➲: edematous gastric glands, ⇨: moderate edema of mucosa, ★: moderate polymorphonuclear cell infiltration, ? : moderately dilated and congested blood vessel, x100. GSG, sham operation group; GIR, ischemia-reperfusion group; GRID, ischemia-reperfusion+5 mg/kg desloratadine group.

Fig 1: Histopathological analysis of stomach tissues of the study groups.

Table 2: Analysis results of histopathological scoring in stomach tissues of animal groups.

Variables	GSG	GIR	GIRD	H/*p*
	Median (minimum-maximum)			
Mucosal degeneration	0(0-0)a	3(2-3)b	0.5(0-1)c	90.261/0.001
Dilation / Congestion	0(0-0)a	3(2-3)b	2(0-3)c	89.819/0.001
PMNL infiltration	0(0-0)a	3(1-3)b	2(1-3)c	86.810/0.001
Mucosal edema	0(0-0)a	3(2-3)b	2(1-3)c	94.309/0.001

abc: p<0.05, different letters on the same line show significant difference between groups. 0: No injury, 1: Mild injury, 2: Moderate injury and 3: Severe injury. PMNL; Polymorphonuclear leukocytes, GSG: Sham operation group; GIR: Ischemia-reperfusion group; GIRD, Ischemia-reperfusion+5 mg/kg desloratadine group. Statistical analysis was done with Kruskal-Wallis test, pairwise comparison was made with Dunn test.

normalized the decrease in CAT levels due to allergic rhinitis (Sadowska-Woda *et al*., 2010a). Desloratadine was also documented to inhibit the synthesis and release of inflammatory mediators and cytokines (Cassano *et al*., 2006). Previous studies also revealed that suppression of basal and histamine-stimulated NF-κB expression played a role in this inhibition (Kocaturk *et al*., 2020). In our study, the increase in IL-6 levels in animals treated with I/R was inhibited by desloratadine, which is similar to the results of Jie *et al*. (2015) study.

Desloratadine attenuated histopathological injury as well as biochemical parameters. When the samples related to GIRD group treated with desloratadine were analyzed, it was determined that there was moderate edema in normal surface epithelium and mucous membranes and glandular bases, moderate level dilatation and congestion in blood vessels and moderate level PMNL infiltration in the areas around the blood vessel (Fig 1C and Table 2). Kocaturk *et al*. (2020). also reported that desloratadine protected the kidney tissue from I/R injury. Tatar *et al*. (2015) revealed that desloratadine alleviated the oxidative stress induced histopathological injury in the submandibular gland.

CONCLUSION

I/R treatment caused oxidative and inflammatory injury in the gastric tissue of animals. Desloratadine prevented the increase of I/R and oxidant and proinflammatory cytokines and the decrease of antioxidants in the gastric tissue and attenuated the histopathological injury. This information suggested that desloratadine was possible to be beneficial in attenuating IR-induced oxidative gastric injury.

Conflict of interest

The authors declared no conflict of interest.

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