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Research Article
Is Benidipine Effective in Preventing Gastric Ischemia/Reperfusion Injury?

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Abstract

Background and Objective: The preventive effect of benidipine on organs and tissues against oxidative and proinflammatory cytokine damage, whose production is elevated by I/R, has been demonstrated. The current study noted that benidipine affects the biochemical and histopathological effects of I/R therapy on gastric injury in rats. **Materials and Methods:** A total of 18 rats were divided into either a Sham operation group (SG), gastric ischemia/reperfusion (GIR) group or benidipine+gastric ischemia/reperfusion (BGIR) groups. Biochemical measures and histological exams were done in all three groups after I/R intervention. **Results:** The MDA, TNF-α, IL-1β and COX2 levels were significantly higher ($p<0.001$) in GIR compared to SG and BGIR, although tGSH and COX1 were significantly lower ($p<0.001$). The SG group was histopathologically normal. The surface epithelium broke off in spots, causing mild degeneration, the gland recesses were decreased, the gland neck areas were wide, the base areas were significantly oedematous and the blood capillaries showed moderate dilatation and congestion in the GIR group. Infiltration of polymorphonuclear cells was seen in the connective tissue surrounding the arteries and close to the gland bases. The BGIR group's histopathological results were not normal, although they were milder than the GIR group's. **Conclusion:** The results discovered that benidipine shifted the oxidant/antioxidant balance in I/R damage in favour of antioxidants, as well as the COX-1/COX-2 equilibrium in favour of COX-2, which is cytoprotective. It appears that administering benidipine for antioxidant and cytoprotective purposes before surgical operations that are likely to cause I/R damage may be advantageous.

Key words: Oxidative stress, benidipine, gastric tissue, ischemia/reperfusion, reactive oxygen species, antioxidant, anti-inflammatory

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Ischemia-reperfusion (I/R) damage is a multi-step pathogenic process that starts with tissue oxygen deprivation, progresses through the formation of free oxygen radicals and culminates in an inflammatory response[1]. Reperfusion (re-blooding) is the presentation of oxygen to the ischemic tissues with a substantial volume of blood, whereas ischemia is the lack of oxygen in the tissues as a result of a reduction or full cessation of blood supply to the tissues for different causes[2]. Hypoxanthine and xanthine oxidase (XO), which accumulate in an oxygen-free environment, cause the formation of highly Reactive Oxygen Species (ROS) with the abundant oxygen offered during the reperfusion period[3]. These Reactive Oxygen Species (ROSs), also known as reperfusion mediators, oxidize cellular membranes lipids (LPO), causing hazardous chemicals such as aldehyde and malondialdehyde (MDA) to develop[1]. Also, it has been shown that one of the other factors that play a major role in the pathogenesis of I/R injury is polymorphonuclear leukocytes (PML)[4]. The PMLs contain oxidant myeloperoxidase (MPO) and other extracts in their azurophilic granules[5]. The MPO released from activated PMLs provides reduction of hydrogen peroxide and chloride ions to hypochlorous acid. Hypochlorous acid is a powerful oxidant that reacts readily with a wide range of biological substances[6]. As known, increased intracellular calcium plays an important role in tissue I/R damage[1]. It has been reported that calcium ions increase ROS production with both xanthine oxidase and cyclooxygenase-2 expression[1,7]. In a range of diseases, including myocardial infarction, ischemic stroke, acute renal damage, trauma and circulatory arrest, I/R adds to morbidity and death. In addition, I/R, which is usual during organ transplantation as well as cardiothoracic, vascular and general surgery, might result in significant problems[8]. The I/R injury of gastric tissue is a critically important problem that develops in more than 80% of patients undergoing surgery[9]. This literature shows that antioxidant and anti-inflammatory drug therapy is required in the pre-and post-operational period to protect the stomach from I/R injury. Also, it supports our thought that calcium channel blockers may be useful in the treatment of the pathogenesis of I/R injury.

Benidipine was planned to test its protective impact against gastric I/R damage in this study both as an L-type and T-type calcium channel blocker antihypertensive drug[10]. It has been shown in the tests that Benidipine protects organs and tissues from oxidant and proinflammatory cytokine damage, whose production is increased by I/R[11-13]. However, no research on the effect of benidipine on I/R-induced oxidative and inflammatory gastric damage has been reported. According to the literature, benidipine might be beneficial in the treatment of gastric damage caused by I/R procedures. As a result, the goal of this study was to see how benidipine affects the histopathologic effects of I/R therapy on gastric injury in rats.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Pharmacology, Experimental Animal Lab, Erzincan, Turkey from February to March, 2022.

Animals: The test used a total of 18 albino Wistar male rats ranging between 290 and 300 g. The Binali Yildirim University Medical Experimental Application and Research Centre provided all of the rats. Animals were kept and fed in pairs at room temp (22°C) for 12 hrs of daylight and 12 hrs of dark before to the test. Animal studies were carried out in compliance with the National Guidelines for the Use and Care of Laboratory Animals and were authorized by Erzincan Binali Yildirim University's local animal ethics committee (Number: 2022/01/06 Dated: 27.01.2022).

Chemicals: Thiopental sodium used in this study was provided from IE Ulagay-Turkey and the commercial formula of benidipine was provided from Deva-Turkey.

Experiment groups: The animals were separated into three groups: Those who had gastric ischemia-reperfusion (GIR), those who received 4 mg kg^{-1} benidipine+gastric ischemia-reperfusion (BGIR) and those who received a sham procedure (SG).

Anaesthesia procedure: All surgical operations were carried out in a sterile environment. About 25 mg kg^{-1} thiopental sodium was given intraperitoneally (i.p.) and xylazine was sniffed at suitable intervals to produce anaesthesia. Rats were kept for some time after receiving thiopental sodium injections to allow for surgical intervention. When the animals were immobilized in the supine position, surgery began[14].

Experimental procedure: About 4 mg kg^{-1} benidipine was delivered orally to the stomach by gavage in the BGIR group of test animals. The GIR and SG groups were both treated with distilled water as a solvent. All rat groups were anaesthetized as described above one hour after receiving benidipine and distilled water. During the anaesthetic phase, a 2.5 cm long midline incision was used to access the stomach and a

laparotomy was conducted. Then, in the BGIR and GIR animal groups, a clip was inserted on the celiac artery and one hour of ischemia and three hours of reperfusion were performed. The incised abdominal area of the SG group was sutured without clipping the celiac artery as in the study of Filaretova *et al.*[15]. All animals were killed with high-dose (50 mg kg^{-1}) thiopental anaesthesia 3 hrs after reperfusion. The gastric tissues collected from the dead animals were then subjected to histopathologic analyses. The histopathologic outcomes from the test were compared and assessed between the groups.

Biochemical analyses

Quantification of tissue malondialdehyde (MDA) and total glutathione (tGSH): The absorbance of the pink-coloured complex formed by thiobarbituric acid (TBA) and MDA was measured spectrophotometrically, as in prior investigations, to determine MDA[16,17]. The tGSH was determined using a procedure similar to that described in earlier papers[18,19].

Quantification of tissue interleukin 1-beta (IL-1β) and tumour necrosis factor-alpha (TNF-α): Analysis of IL-1β and TNF-α levels in homogenates obtained from gastric tissue was performed with ELISA immunoassay kits (YHB1098Ra, Shanghai LZ) according to the instructions from the manufacturer.

Determination of issue cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) activity: The COX-1 and COX-2 activities in gastric tissue were measured using the assay kit (Item No. 760151, Cayman, Ann Arbor, MI, USA).

Histopathological evaluation: The animals' tissues were preserved in a 10% formaldehyde solution for 72 hrs. The materials were placed in the cassette after being fixed and rinsed in running water for 24 hrs, after which they were dried by passing through an escalating series of alcohols (70, 80, 90 and 100%). Stomach tissues were cleaned in xylol before being embedded in paraffin blocks and cut into 4-5 micron thick pieces. The sections were stained with haematoxylin and eosin dual staining, assessed and photographed using Olympus DP2-SAL software (Olympus® Inc. Tokyo, Japan). Six locations, one central and five peripheries, were selected at 100× magnification in six sections for each test group in the sequences obtained. Mucosal degeneration, vascular dilatation/congestion (occlusion), polymorphonuclear cell infiltration and mucosal oedema were used to assess deviations from normal histological tissue structure. For the stated criteria, scoring ranged from 0 to 3 points (0 = none, 1 = mild, 2 = moderate and 3 = severe). For the study groups, a double-blinded histologist evaluated their histopathology.

RESULTS

Biochemical findings: The MDA, TNF-α, IL-1β and COX-2 levels were observed to be higher in the GIR group than in the SG group ($p<0.001$). When compared to the GIR group, they were shown to be lower in the BGIR group ($p<0.001$), but in IL-1β ($p = 0.140$), MDA ($p = 0.197$), TNF-α ($p = 0.002$) levels there was no difference between the two groups when compared to the SG group. The COX-2 levels in the BGIR group were found to be greater than in the SG group ($p<0.001$). The TNF-α and COX-1 levels in the GIR group were found to be higher than in the SG group ($p<0.001$). The BGIR group had lower TNF-α and COX-1 levels than the GIR group ($p<0.001$), but there was no significant difference between the groups when compared to the SG group ($p = 0.002$, $p = 0.233$) (Table 1). Biochemical findings were shown in Fig. 1 and 2.

When the histopathological evaluation findings were examined, it was found that the mean degeneration level was higher in the GIR compared to the SG ($p<0.001$). In the BGIR, the mean degeneration level was found to be lower compared to the GIR ($p<0.001$), while higher compared to the SG group ($p = 0.001$). The GIR group had significantly greater mean dilatation and congestion, mean PMNL infiltration and mean

Table 1: Biochemical findings according to the groups

	Groups			Pairwise comparisons p-values		
	SG (1)	GIR (2)	BGIR (3)	1 vs 2	1 vs 3	2 vs 3
MDA (μmol/g prot)	4.25±0.08	7.13±0.24	4.49±0.30	<0.001	0.197	<0.001
tGSH (nmol/g prot)	9.16±0.11	6.46±0.11	8.85±0.08	<0.001	<0.001	<0.001
TNF-α	3.12±0.07	5.87±0.09	3.34±0.09	<0.001	0.002	<0.001
IL-1β	2.65±0.16	4.73±0.13	2.81±0.09	<0.001	0.140	<0.001
COX-1	4.18±0.11	1.77±0.20	3.98±0.26	<0.001	0.233	<0.001
COX-2	0.24±0.04	5.21±0.48	1.41±0.14	<0.001	<0.001	<0.001

*Kruskal Wallis test was performed with Tukey test as *post hoc*, results were presented as Mean±Standard deviation, SG: Sham operation group, GIR: Gastric ischemia/reperfusion group and BGIR: benidipine+gastric ischemia/reperfusion group

Table 2: Histopathological findings according to the groups

	Groups			Pairwise comparisons p-values		
	SG (1)	GIR (2)	BGIR (3)	1 vs 2	1 vs 3	2 vs 3
Mean degeneration	0.00±0.00	2.22±0.52	1.13±0.45	<0.001	<0.001	0.001
Mean dilatation-congestion	0.00±0.00	1.86±0.51	0.55±0.49	<0.001	0.078	<0.001
Mean PMNL infiltration	0.00±0.00	2.52±0.32	0.47±0.42	<0.001	0.046	<0.001
Mean mucosal edema	0.00±0.00	2.72±0.45	0.63±0.46	<0.001	0.026	<0.001

*Kruskal Wallis test was performed with Tukey test as *post hoc*, results were presented as Mean±Standard deviation, SG: Sham operation group, GIR: Gastric ischemia/reperfusion group and BGIR: benidipine+gastric ischemia/reperfusion group

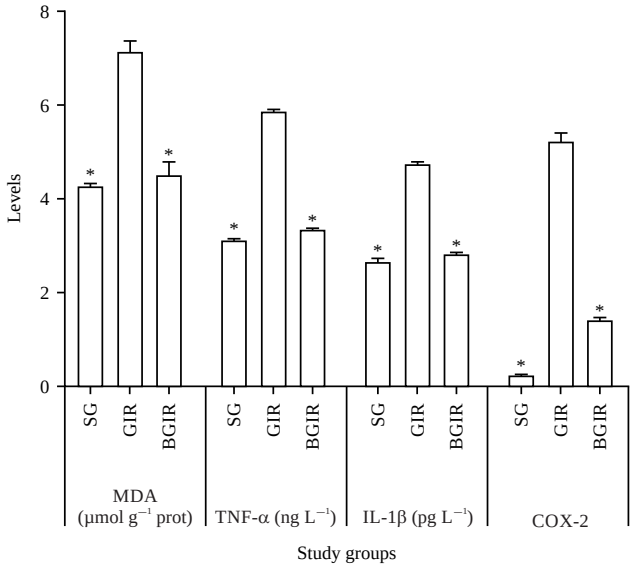

Fig. 1: Levels of oxydant MDA, TNF-α, IL-1β and COX2 in SG, GIR and BGIR groups
*p<0.001

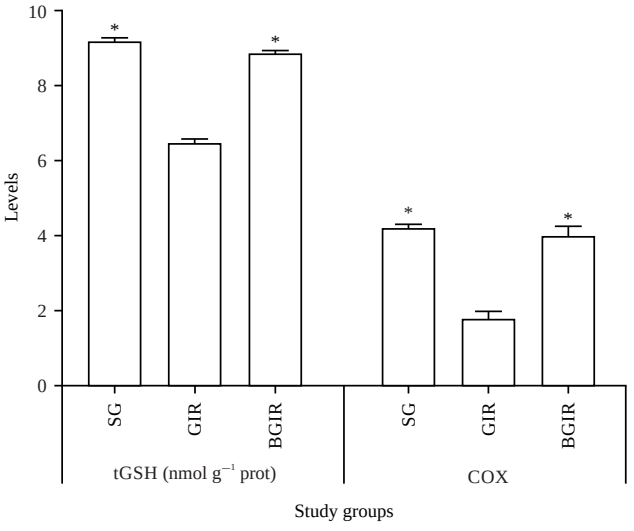

Fig. 2: Levels of antioxydant tGSH and COX1 in SG, GIR and BGIR groups
*p<0.001

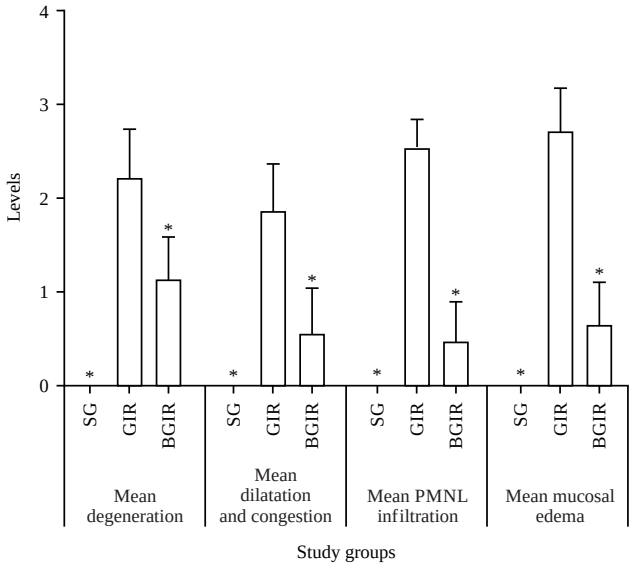

Fig. 3: Histopathological findings in SG, GIR and BGIR groups
*p<0.001

mucosal oedema than the SG group (p<0.001). The mean values in the BGIR group were found to be lower than in the GIR group (p<0.001). However, there was no statistically significant difference in mean dilatation and congestion, mean PMNL infiltration or mean mucosal oedema levels between the SG and BGIR (Table 2).

Histopathological findings: Histopathological findings were shown in Fig. 3. In the histopathological assessment of the gastric tissue sections of the SG group which underwent a sham operation, it was observed that the adventitia mucosa surface epithelium and glands, as well as normal gastric stratification and wall structure, were of normal histological architecture (Fig. 4).

The surface epithelium broke off in places, causing moderate degeneration, the gland recesses were reduced, the gland neck regions were opened, the base areas were seriously oedematous and the blood capillaries showed moderate dilatation and congestion in the GIR group's sections where only I/R was applied to the stomach. In the

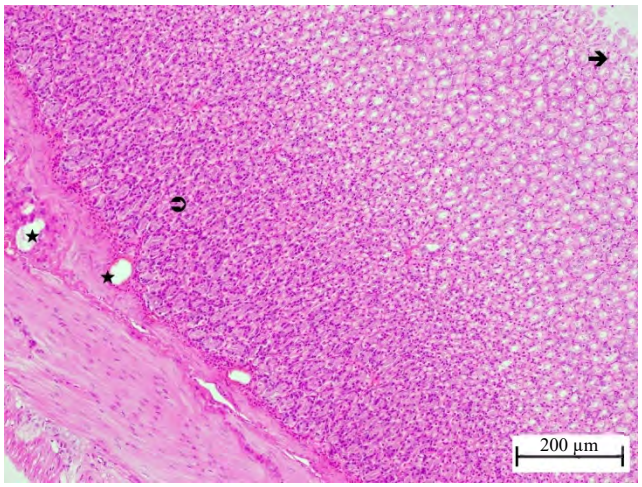

Fig. 4: Hematoxylin-eosin staining in gastric tissue belonging to the SG group
➔: Surface epithelium, ➲: Gastric glands, ★: Blood vessel (HE×100)

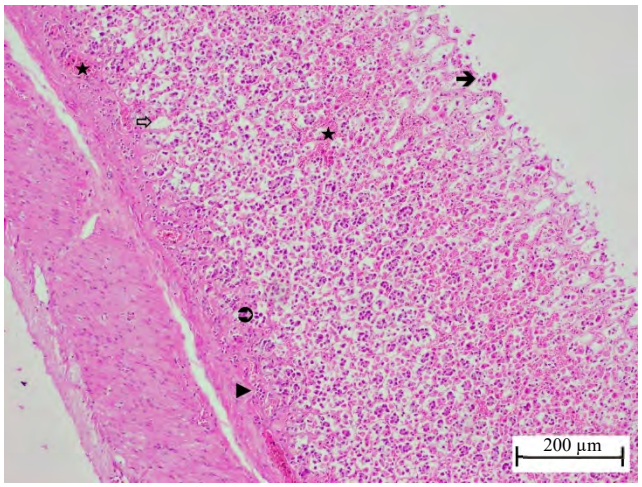

Fig. 5: Hematoxylin-eosin staining in gastric tissue belonging to the GIR group
➔: Locally exfoliated and degenerated surface epithelium, ➲: Severe edematous gastric glands, ⇨: Severe oedema of the mucosa, ►: Severe polymorphonuclear cell infiltration, ★: Moderately dilated and congested blood vessel (HE×100)

connective tissue region around the arteries and next to the gland bases, there was substantial polymorphonuclear cell infiltration in the samples from this group (Fig. 5).

When the samples from the BGIR group that had been given benidipine were analyzed, it was determined that the surface epithelium was mildly degenerated, mild oedema in the mucosa and gland bases, mild dilatation and congestion in the blood vessels and a small amount of polymorphonuclear cell infiltration in the areas around the blood vessel (Fig. 6).

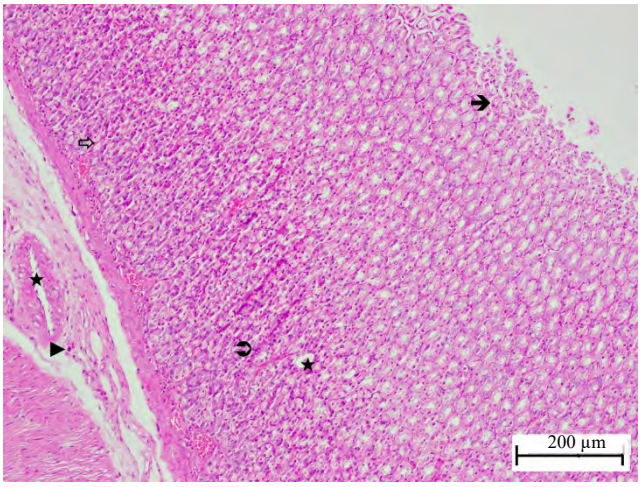

Fig. 6: Hematoxylin-eosin staining in stomach tissue belonging to BGIR group
➔: Slightly degenerated surface epithelium, ➲: Mildly edematous gastric glands, ⇨: Mild oedema of the mucosa, ►: weak polymorphonuclear cell infiltration, ★: Weak to moderately dilated and congested blood vessel (HE×100)

DISCUSSION

In this study, the possible benefit of Benidipine was examined, a calcium channel blocker, on ischemia/reperfusion injury that may occur in gastric tissue. Experimentally, we examined the gastric tissues obtained by clamping the celiac artery for 1 hr and then providing reperfusion, similar to what Cimen *et al.*[20] did in liver tissue, biochemically and histopathologically.

Cimen *et al.*[21] concluded in another study that benidipine prevents I/R injury in the liver. Similarly, in this study, it was observed that benidipine can protect cells from I/R damage as a result of both biochemical and histopathological examinations.

Calcium influx into the tissues increases during ischemia and it has been observed that ROS production in the tissues increases with subsequent tissue blood supply. It is known that at this stage, products such as MDA emerge as a result of damage to the tissues and these products further increase tissue damage[22,23].

An increase in ROS derivatives due to increased xanthine oxidase level in ischemia/reperfusion injury and an increase in MDA with an increase in intracellular calcium have been reported in previous studies[24]. However, studies showing that cytokines that are pro-inflammatory such as TNF-α and Il-1β increase in case of ischemia-reperfusion injury are also included in the literature[25,26]. In this study, the result showed

that Il-1β, MDA and TNF-α levels were higher in the GIR group compared to the SG group and were lower in the BGIR group administered with benidipine at levels close to the SG group, in line with the literature.

There were studies in the literature that tGSH protects cells from oxygen radicals and that its concentration in cells increases during I/R injury[27,28]. Similarly, in this study, tGSH level was found to be lower in the GIR group, which was exposed to I/R, compared to the SG group. In the BGIR group, the tGSH level was found to be close to the SG group and significantly higher than the GIR group.

In a study by Demiryilmaz *et al.*[14] investigating I/R damage in the liver, it was determined that the balance between COX-1 and COX-2 changed in I/R damage. While the COX-1 enzyme is responsible for the production of prostaglandins with cytoprotective properties, COX-2, on the contrary, takes an active role in the synthesis of proinflammatory cytokines[29]. In this study, it is found that, a decrease in COX-1 levels and an increase in COX-2 levels in the GIR group that underwent I/R injury compared to the SG group. Results showed that the cytoprotective COX-1 level was increased and the proinflammatory COX-2 level was decreased in the BGIR group administered with Benidipine.

It has been shown in many studies that cell degeneration, dilatation-congestion, PML infiltration and tissue oedema occur in I/R injury[20,21]. The surface epithelium broke off in spots, causing mild degeneration, the gland recesses were diminished, the gland neck areas were opened, the base areas were badly oedematous and the blood capillaries exhibited moderate dilatation and congestion in the GIR group's sections. In the connective tissue region around the arteries and next to the gland bases, there was substantial polymorphonuclear cell infiltration in the samples from this group. When the tissues belonging to the BGIR group treated with benidipine were evaluated, it was determined that the surface epithelium was mildly degenerated, mild oedema in the mucosa and gland bases, mild dilatation and congestion in the blood vessels and a small amount of polymorphonuclear cell infiltration in the areas around the blood vessel. This supported the idea that benidipine protects cells from I/R damage and is compatible with biochemical analyses.

The current study has various limitations that should be noted. Since this study is an experimental animal study, the number of experimental animals was kept low in terms of animal rights. Another limitation is that experimental animal studies need to be supported by human studies in the future, due to the variability caused by species differences.

CONCLUSION

The results showed that benidipine influenced positively the oxidant/antioxidant balance that occurs in I/R injury in the direction of antioxidant and the balance of COX-1/COX-2 in favour of COX-2, which is cytoprotective. It suggested that the administration of benidipine for antioxidant and cytoprotective purposes before surgical procedures with expected I/R damage will be beneficial.

SIGNIFICANCE STATEMENT

This study discovers the protective effect of benidipine against Ischemia/Reperfusion injury in gastric tissue of rats. This study will help researchers with an idea about the role of benidipine in preventing ischemia/reperfusion injury in their future studies and it will also be a guide for future studies.

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