

Protective effect of vitamin E on gastric mucosal injury in rats with biliary obstruction

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NZ Cantürk, Z Cantürk, G Özbilim, C Yenisey. Protective effect of vitamin E on gastric mucosal injury in rats with biliary obstruction. *Can J Gastroenterol* 2000;14(6):499-503. Patients with liver disease display increased susceptibility to gastric mucosal damage. A role of free radicals has been suggested in the development of gastric mucosal damage in normal subjects. The effects of antioxidant vitamin E treatment on the liver and stomach in cirrhotic rats were examined.

Fifty rats were divided into three groups. Cirrhosis was induced by bile duct ligation in 40 of 50 rats. Controls underwent a sham operation. Gastric mucosal lesions were produced by intragastric administration of 1 mL of 95% ethanol in all three groups. Twenty bile duct-ligated rats were injected intramuscularly with vitamin E (100 mg/kg/day). Liver and stomach histology, and stomach malondialdehyde and glutathione levels were determined. Portal hypertension was measured.

Macroscopic and microscopic gastric mucosal injury were significantly greater in the control and common bile duct-ligated groups than in the vitamin E-pretreated group ($P < 0.05$). The tissue malondialdehyde and glutathione levels were significantly decreased in the vitamin E-administrated group compared with the common bile duct-ligated group ($P < 0.001$). Vitamin E administration may be cytoprotective for both the liver and gastric mucosa in bile duct-ligated rats.

Key Words: Antioxidant; Free radicals; Obstructive jaundice; Stomach; Vitamin E

Effet protecteur de la vitamine E sur les lésions de la muqueuse gastrique chez des rats atteints d'obstruction biliaire

RÉSUMÉ : Les patients atteints d'une maladie du foie sont plus exposés à développer des lésions de la muqueuse gastrique. Le rôle de radicaux libres dans le développement de ce type de lésions chez des sujets sains a été évoqué. Les effets d'un traitement avec l'antioxydant qu'est la vitamine E sur le foie et l'estomac de rats atteints d'une cirrhose ont été étudiés.

On a divisé 50 rats en trois groupes puis, induit une cirrhose chez 40 des 50 rats par ligature du canal cholédoque. Le groupe témoin a subi une opération factice. On a provoqué des lésions de la muqueuse gastrique en administrant 1 mL d'éthanol à 95 % par voie intragastrique aux trois groupes. Vingt rats du groupe au cholédoque ligaturé ont reçu de la vitamine E (100 mg/kg/jour) par voie intramusculaire. On a ensuite procédé à un examen histologique du foie et de l'estomac, mesuré les niveaux de glutathion et de malondialdéhyde de l'estomac et procédé à une mesure de l'hypertension portale.

Les lésions microscopiques et macroscopiques de la muqueuse gastrique étaient nettement plus importantes dans le groupe témoin et dans le groupe au cholédoque ligaturé que dans le groupe prétraité avec de la vitamine E ($p < 0,05$). Les niveaux tissulaires de malondialdéhyde et de glutathion étaient nettement moins élevés dans le groupe qui avait reçu de la vitamine E que dans le groupe au canal cholédoque ligaturé ($p < 0,001$). L'administration de vitamine E pourrait avoir un effet cytoprotecteur à la fois sur la muqueuse gastrique et hépatique des rats au cholédoque ligaturé.

Patients with liver disease display increased susceptibility to gastric mucosal damage, as characterized by hemorrhagic gastropathy and peptic ulceration. In recent years, this damage has been termed 'congestive gastropathy'. It may be responsible for most of the gastrointestinal tract bleeding in patients with liver diseases (1-3).

Because of decreased acid secretion and increased hydrogen ion back diffusion, the gastric mucosa of cirrhotic patients may be sensitive to various noxious stimuli and may be protected by various agents (4-7). In addition, the congestive gastropathy causes hypoxia in the gastric mucosa and releases highly toxic free radicals (8). A previous study

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suggested that oxygen-derived free radicals play a role in the development of acute gastric mucosal lesions induced by bile duct ligation (9). Reduced plasma levels of vitamin E have been reported in patients with cirrhosis (10). Although vitamin E supplementation has been shown to be cytoprotective in several animal models of acute liver disease and in the gastric mucosa of normal rats (10,11), gastric cytoprotective effects of vitamin E administration have not been studied in this model of liver disease. We thought that the experimental model with bile duct ligation showed spontaneous gastric mucosal damage and increased susceptibility to ethanol-induced gastric damage. Therefore, addition of antioxidants may protect the gastric mucosa against these noxious stimuli (12). We previously showed that vitamin E has cytoprotective effects on ethanol-induced hemorrhagic gastropathy in the normal and carbon tetrachloride-induced cirrhotic rat model (11,13).

Our aim in the present study was to demonstrate whether supplementary vitamin E administration afforded gastric protective effects on ethanol-induced hemorrhagic gastritis in the bile duct ligated-rat model.

ANIMALS AND METHODS

All rats were handled in compliance with the Experimental Surgery Department of Cumhuriyet University, Turkey. The study was approved by the ethical committee of Cumhuriyet University and performed with standard guidelines for care and use of laboratory animals. Rats were kept in stainless steel cages, given food and water ad libitum, and quarantined seven days before surgery. All rats were subjected to a 12 h light-dark cycle. The animals were weighed just before the experiment; their mean weight was 212 g. At the beginning of the study, rats were randomly divided into three groups: group I, control (n=10); group II, the common bile duct-ligated (CBDL) group (n=20); and group III, the CBDL and vitamin E group (n=20). Vitamin E (Roche Ltd, Basel, Switzerland) was injected intramuscularly (100 mg/kg/day) to group III throughout the study. The procedure for CBDL was as follows. Animals were anesthetized with ketamine hydrochloride and xylazine. The abdomen was opened by median incision, and the common bile duct (CBD) was exposed. The CBD was ligated by two single ligatures – proximally as close as possible to the liver and distally as close as possible to the duodenum. A portion of the CBD between ligatures was cut. At the third week of CBDL, all rats in each group were fasted for 24 h. Portal pressure was measured in each rat of each group. A PE 50 tube for each rat was inserted via a large pericolic mesenter tributary, and pressure was measured from the level of the vena cava to the tip of a column of saline within the tubing. Gastric mucosal injury was produced by instillation of absolute alcohol via an orogastric tube. Three hours later, all animals were sacrificed; the stomachs were excised along the greater curvature and inspected for macroscopic damage, and each stomach was then cut into grips obliquely across the entire corpus. Macroscopic areas of gastric mucosal injury were assessed by an uninformed observer as follows: grade 0, normal; grade 1, erosions on one-

third of the stomach; grade 2, erosions on two-thirds of the stomach; and grade 3, erosions on the entire stomach. The gastric mucosal lesions (erosions) were recognized using a dissecting microscope with $\times 10$ magnification. The scattered dark areas were gastric lesions that were recognized macroscopically as depressions due to breaks in the mucosa. Each stomach was cut into grips obliquely across the entire corpus, fixed in buffered formalin, and stained with hematoxylin and eosin. Specimens were evaluated by light microscopy and graded as follows: grade 0, normal; grade 0.5, polymorphonuclear cell infiltration into the lamina propria; grade 1, mild edema, hyperemia and acute inflammation in the lamina propria; grade 2, slight light hemorrhage, mucosal erosion, hyperemia and acute inflammation; and grade 3, diffused mucosal erosion, severe edema, hyperemia and hemorrhage. Cirrhosis of the liver was evaluated by gross inspection and by microscopic examination of liver.

Determination of tissue malondialdehyde level: Part of the removed specimens of stomach was washed with saline and stored at -70°C . Tissues were homogenized by cold trichloroacetic acid (TCA) (1 g tissue plus 1 mL 10% TCA plus 8 mL 5% TCA). Homogenates were centrifuged at 2600 g for 15 mins, and 1 mL of supernatant was mixed with 0.6% TCA. The resulting mixture was heated to 100°C for 10 mins and cooled for 5 mins in ice; spectrophotometric analysis was performed at 532 nm. Data were multiplied by the molar extinction coefficient of 1.56×10^{-5} (14).

Determination of tissue glutathione level: The homogenate (0.5 mL) of each sample was mixed with 1 mL of a solution containing 100 mM Tris hydrochloric acid (pH 8.2), 1% sodium dodecyl sulphate and 2 mM EDTA. Fifteen milliliters of 5-aminosalicylic acid was added to each sample. The mixture was incubated for 5 mins at 25°C and centrifuged to remove any participant. 5,5'-Dithiobis(2-nitrobenzoate) (45 mL) was then added to each reaction volume and incubated for 15 mins at 37°C to allow for formation of thionitrobenzoic acid (TNB). The absorbency of each sample was determined at 412 nm. RSH content was calculated assuming a molar extinction coefficient of 13,000 at 412 nm for TNB (15).

Results are expressed as means \pm SE. Statistical comparisons (ordinary ANOVA and Tukey Test as post hoc test) were assumed to be significant at $P < 0.05$.

RESULTS

Visual evaluation of the liver indicated cholestatic changes such as congestion and edema of the liver, and dilation of the extrahepatic part of the bile duct in all rats. Histological liver changes were analyzed at the end of the experiment. Marked bile duct proliferation in expanded portal tract, extension of proliferated bile duct into the lobule, mononuclear cell infiltration into the widened portal area, vascular endothelial cell injury and some neutrophil infiltration, intracytoplasmic bile pigment accumulation in hepatocytes, bile pigment accumulation into bile canaliculus in portal area and bile pigment-phagocytosed macrophages in supportive tissue were observed in the CBDL group. There was less

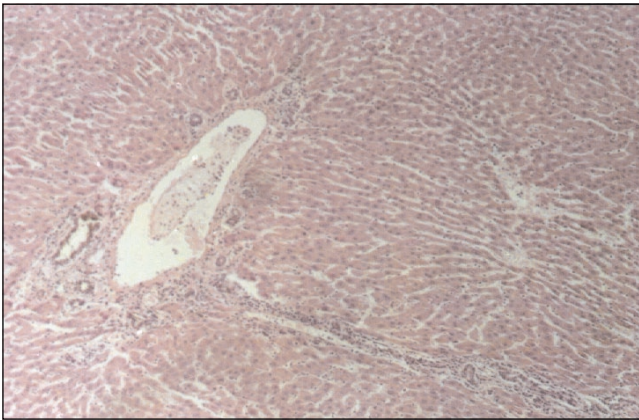


Figure 1) Histological liver samples in common bile duct-ligated (CBDL) groups. Enlarged vessels and massive inflammatory infiltration in the portal area, bile deposition in the biliary canaliculus, inflammatory cell infiltration into sinusoids and intracytoplasmic biliary pigmentation in hepatocyte (hematoxylin and eosin stain; original magnification $\times 20$)

canalicular proliferation and mononuclear cell infiltration in the portal area, and less hepatocyte injury in the CBDL- α -T group. (Figure 1).

Rats with ligated bile ducts had gross evidence of portal hypertension with dilated and tortuous mesenteric veins. Their portal pressure measured 26.2 ± 3.1 cm saline in the CBDL group and 23.9 ± 1.6 in the CBDL plus vitamin E-pretreated group, compared with 17.0 ± 2.4 cm saline in the control group ($P < 0.001$). There were also significant differences between both CBDL groups ($P < 0.05$).

Macroscopic assessment: Macroscopic areas of gastric mucosal injury after ethanol instillation were significantly larger in the control and CBDL groups than in the vitamin E-pretreated group ($P < 0.05$) (Figure 2). There was no significant difference between the control group and the CBDL-vitamin E-pretreated groups ($P > 0.05$) (Table 1).

Microscopic assessment: Microscopic studies demonstrated superficial erosions, minimal focal necrosis of the surface and foveolar cells, severe edema of the lamina propria and submucosa, erythrocyte extravasation, minimal mononuclear cell infiltration, and accompanying degenerative and regenerative changes of the surface and foveolar epithelium in all ethanol-instilled groups.

If mucosal injury after ethanol instillation was considered, superficial damage to the surface epithelial cells with their subsequent desquamation was greater in the CBDL and control groups than in the vitamin E-pretreated group ($P < 0.05$) (Table 1). Although focal mucosal necrosis was superficial damage, it was more extensive in CBDL rats than in the vitamin E-pretreated and the control groups (Figures 3,4).

Biochemical analysis: The results of the three groups are shown in Table 2. By the ligation and cutting of the CBD, malondialdehyde (MDA) levels increased significantly in both CBDL groups compared with the control groups ($P < 0.0001$ and $P < 0.0001$, respectively). The tissue MDA level was significantly decreased in the vitamin E-pretreated group compared with the CBDL group ($P < 0.001$). Glutathione levels increased significantly in the CBDL and

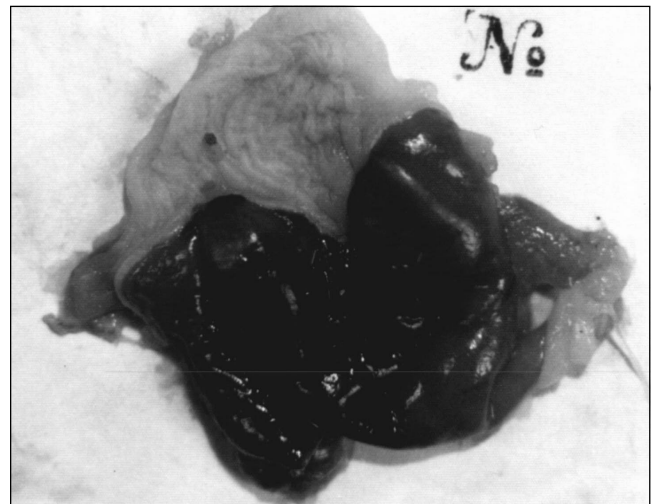
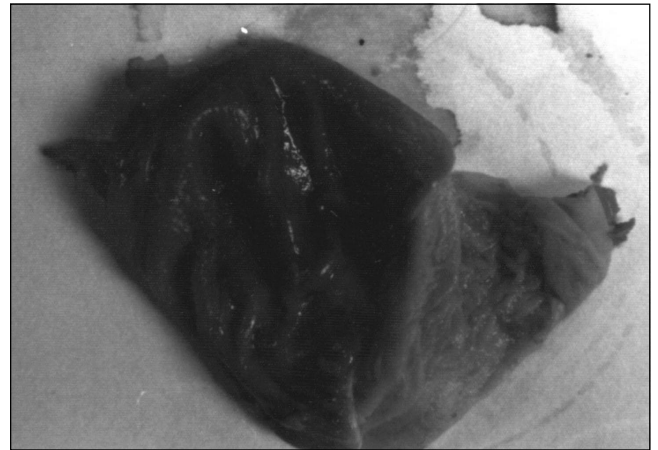


Figure 2) Gross appearance of the stomach. **Top** From the common bile duct-ligated group. **Bottom** From the Vitamin E-pretreated common bile duct-ligated group

TABLE 1
Macroscopic and microscopic scoring for gastric mucosal injury in all groups

	Score for analysis of gastric mucosal injury	
	Macroscopic analysis	Microscopic analysis
Control group	2.20 ± 0.92	2.23 ± 0.95
CBDL group	2.25 ± 0.85	2.50 ± 0.97
CBDL-vitamin E pretreated group	1.40 ± 1.20	1.30 ± 1.30

Macroscopic analysis: $P > 0.05$, control versus CBDL; $P > 0.05$, control versus CBDL-vitamin E-pretreated group; $P < 0.05$, CBDL versus CBDL-vitamin E-pretreated group. Microscopic analysis: $P > 0.05$, control versus CBDL; $P < 0.05$, control versus CBDL-vitamin E-pretreated group; $P < 0.05$, CBDL versus CBDL-vitamin E-pretreated group. CBDL Common bile duct-ligated

CBDL-vitamin E groups compared with the control group ($P < 0.0001$ and $P < 0.0001$, respectively). The tissue glutathione level was significantly decreased in the vitamin E-pretreated group compared with the CBDL group ($P < 0.05$).

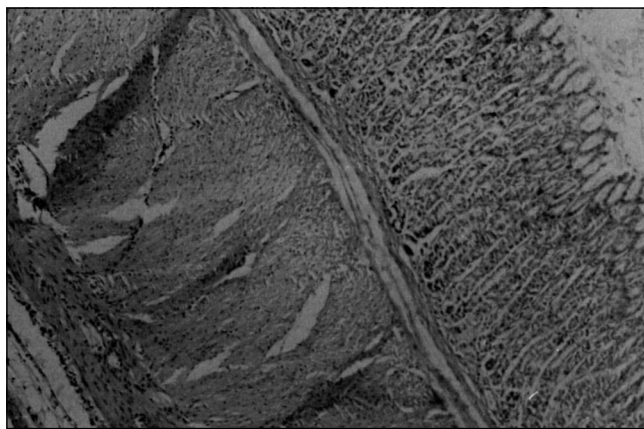


Figure 3) Microscopic appearance of the stomach with cirrhosis of the liver (hematoxylin and eosin stain; original magnification $\times 10$)

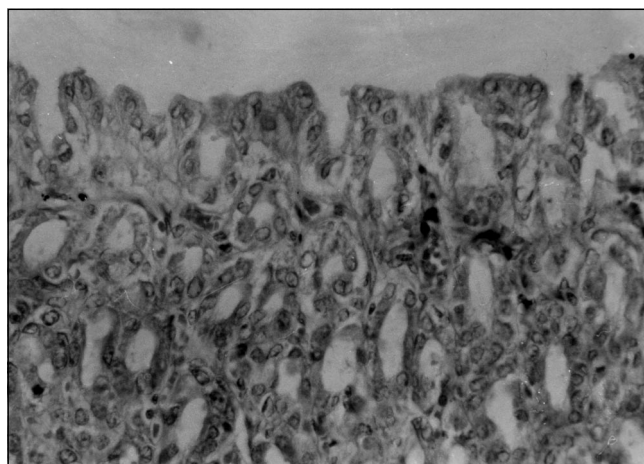


Figure 4) Microscopic appearance of the stomach with vitamin E pretreated cirrhosis of the liver (hematoxylin and eosin stain; magnification $\times 20$)

DISCUSSION

The stomachs of patients with liver disease are frequently subject to a number of alterations, detectable by endoscopy, the presence of which indicates a disturbance in the mucosa. Less is known about factors responsible for these manifestations, although several investigators believe that changed portal flow has an etiopathogenetic role (16,17). Both mild and severe gastropathy in patients with liver disease may be caused by several factors (18). As observed in the present study, histological changes of gastropathy are capillary ectasia with gastric red spot, and with or without inflammatory cellular infiltration and extravasation of red blood cells via a defective part of the endothelial cells (17,19). D'Amico et al (20) reported that mild congestion of superficial capillary vessels was a common feature of mild gastropathy. These well established vascular abnormalities of gastropathy may be explained by the number of hemodynamic factors (18).

The ulcerogenic reaction to stress and chemicals involves the complex interactions between aggressive and protective mechanisms in the gastrointestinal mucosa (21). One of the major factors causing gastrointestinal injury is thought to be

TABLE 2
Stomach malondialdehyde (MDA) and glutathione GSH(x) levels for three groups

	MDA (nmol/g)	GSH(x) (nmol/g)
Control group	11.6 \pm 2.5	18.6 \pm 5.8
CBDL group	36.6 \pm 9.3	43.8 \pm 4.4
CBDL-vitamin E pretreated group	31.7 \pm 8.3	35.7 \pm 6.1

For MDA, control versus common bile duct -ligated (CBDL) group, $P < 0.0001$; control versus CBDL-vitamin E pretreated group, $P < 0.0001$, CBDL versus CBDL-vitamin E pretreated group, $P < 0.01$. For GSH(x), control versus CBDL, $P < 0.0001$; control versus CBDL-vitamin E pretreated group, $P < 0.0001$, CBDL versus CBDL-vitamin E pretreated group, $P < 0.05$

the excessive generation of oxygen-derived free radicals, which overwhelm the endogenous antioxidant defense system (22,23). Vitamin E is a free radical scavenger and prevents the propagation of the peroxidative process (24). Fat soluble vitamins are particularly prone to deficiency during cholestasis (25). Because vitamin E, like other fat soluble vitamins, may be poorly absorbed if any phase of fat digestion, absorption or transport is interrupted, tissue vitamin E levels decrease during chronic cholestasis (25-27); however, symptoms due to vitamin E deficiency have not been reported during the early phase of obstructive jaundice, and the effects of this deficiency are under discussion (28). In previous studies, a cytoprotective effect of vitamin E was demonstrated in a CBDL experimental rat model (29).

The results of the present investigation have demonstrated that pretreatment of bile duct-ligated rats with vitamin E alone markedly ameliorates gastric mucosal damage induced by absolute ethanol. A number of investigators have observed signs of vitamin E deficiency in conditions of stress (22,30). Protection of the gastric mucosa by vitamin E may to some extent be attributed to its antisecretory activities. The mechanism by which vitamin E decreases gastric acid secretion is not clearly understood (30). Vitamin E has been shown to decrease calcium influx across the cell membrane (31) and to increase the level of the vasodilator prostacyclin (32). Oxygen-derived free radicals have been implicated in gastric mucosal lesions induced by various necrotizing agents (33). Vitamin E has been observed to restrict the formation of peroxides, possibly due to neutralizing free radicals (12,33) and stabilizing biological membranes in general, in a manner unrelated to its antioxidant property (34). Gastric ulceration was enhanced in rats with obstructive jaundice, probably because of compromised defensive factors. Prophylaxis of acute gastric ulceration with or without obstructive jaundice may not be attained by vagotomy alone; an adequate maintenance of defensive factors seems to be also necessary (35).

Although the addition of bile acid or bilirubin to the serosal solution under experimental conditions is not the same as obstructive jaundice, studies suggest that the inhibition of bicarbonate secretion in the gastric mucosa may have an important role in the formation of acute gastric mucosal lesions

in obstructive jaundice (36). In the present study, we examined the role of oxygen-derived free radicals in the pathogenesis of acute gastric mucosal lesions induced by obstructive jaundice in rats. As reported previously, our results suggest that oxygen-derived free radicals play a role in the development of acute gastric mucosal lesions induced by

obstructive jaundice (9). Finally, our findings showed that vitamin E supplementation provided better protection to the gastric mucosa in a rat model of biliary obstruction-induced cirrhosis. Further multidose studies are necessary to determine the optimal and safe doses of vitamin E against congestive gastropathy.

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