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Examination of pathological and biochemical findings of the damage caused by liver retraction during abdominal surgeries using an experimental model

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During operations such as those involving the hepatobiliary system, stomach, and gastroesophageal junction, hepatic retraction is needed to visualize the operation field. Hepatic tissue resources are critically important, particularly during operations performed in infants with biliary atresia. We observed that patients' serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) levels increased after these operations.

It is known that ALT, AST, and LDH blood levels increase in humans in hepatic injury.[1,2] Thus, ALT, AST, and LDH values are good indicators for hepatic injury and have been used to evaluate hepatic injury in previous studies.[3-14] It has been shown that for open surgery, ALT, AST, and LDH blood levels increased during gastric and biliary system operations more than other operations.[3-6] Retraction or local trauma is thought to be the cause.

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Abstract

Objectives: This study aims to determine whether hepatic retraction during abdominal surgery causes damage to the hepatic tissue.

Materials and methods: Thirty Sprague-Dawley rats (mean weight: 227.3±13.2 g; range, 200 to 250 g) were allocated to the following four groups: *(i)* the control group; *(ii)* the retraction group, in which pressure was applied to the liver with Farabeuf's retractor; *(iii)* the crush group, in which the liver was crushed with a bulldog clamp; and *(iv)* the deviation group, in which the liver was deviated cranially as creating angling to vascular structures. A liver tissue sample was taken for pathological and biochemical examination. Blood samples were collected for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) measurements.

Results: The crush group showed a significant elevation of serum ALT, AST, and LDH levels, decreased tissue glutathione levels, increased malondialdehyde levels, severe sinusoidal dilatation/congestion, and necroinflammatory focus in the postoperative histopathological findings. The deviation group showed elevation in serum ALT levels, sinusoidal dilatation/congestion, and necroinflammatory focus postoperatively. According to the histopathological findings, although balloon cell degeneration, sinusoidal dilatation/congestion, and necroinflammatory focus were still observed on the 28th day in the retraction, crush, and deviation groups; however, the difference did not show statistical significance with the control group.

Conclusion: We found that the crush mechanism was more harmful to the liver tissue than the angling of vascular structures. We recommend keeping the hepatic retractions at minimum tension during the surgical procedures to protect the liver tissue, particularly in patients with limited liver function, such as cirrhotic patients and newborns with biliary atresia.

Keywords: Abdominal, damage, hepatic, retraction, surgery.

Clinical studies also investigate the mechanism of hepatic enzyme increase after laparoscopic cholecystectomy. In these studies, hepatic enzyme levels of patients undergoing different operations were compared.[7-14] The results were conflicting; some authors mentioned that the increases in hepatic enzyme levels were due to increased intra-abdominal carbon dioxide pressure leading to decreased splanchnic blood flow,[7-10] while others stated that the increase in hepatic enzyme levels might be secondary to hepatic retraction.[3,5,6,11,12] Additionally, some stated that the increase in hepatic enzymes could be multifactorial, including both the increase in intraabdominal pressure and the squeeze pressure effect of the traction.[15] These data raise the question about the presence of hepatic tissue injury and its contemporary damage to the liver during hepatic retraction.

The mechanism of hepatic retraction can be divided into "crush" due to pressure applied to liver tissue or "deviation" due to cranial deviation of the liver, causing angling in the vascular system. If there is damage to hepatic tissue, which of these mechanisms should be cited as the cause? To resolve this question, we separately simulated hepatic retraction, crush, and deviation in rats.

A few studies investigating whether hepatic retraction is harmful to the hepatic tissue were found in the available literature.[5,16] The present study aimed to determine whether hepatic retraction during upper abdominal surgery causes long-term damage to the hepatic tissue. If damage was present, we also aimed to find answers to the mechanism responsible. If we could understand the mechanism of damage, we could think about ways of decreasing the damage to the liver, particularly in already damaged liver tissue, such as in biliary atresia and cirrhosis cases.

MATERIALS AND METHODS

Thirty Sprague-Dawley rats (mean weight: 227.3±13.2 g; range, 200 to 250 g) were included in the study. The number of rats required to be in the groups was calculated by a biostatistician while preparing the experimental project. The Experimental Research Center of the Medical Faculty of Başkent University provided the rats. The rats were housed in a windowless animal quarter with automatically controlled temperature (22±2°C) and illumination (light on at 7:00 AM and off at 9:00 PM; 14-h light, 10-h dark cycle). Humidity ranged from 50 to 55%. Rats were fed with standard rat chow and tap water ad libitum. The lost or severely ill rats were excluded from the study. The study protocol was approved by Başkent Ethical Committee for Experimental Research on Animals (Data: 26.04.2010, No: 10/14).

Thirty animals were allocated to the following four groups: *(i)* the control group (n=6), in which no interventions were done; *(ii)* retraction group (n=8), in which retraction was applied to the liver with Farabeuf's retractor for 30 min (a wet sponge was placed between the retractor and liver and a weight of 100 g was hung on the retractor part outside the abdomen with a suture thread to provide constant retraction for 30 min; Figure 1); *(iii)* the crush group (n=8), in which the liver was crushed with a flat surface bulldog clamp for 30 min without angling the vascular structures (a wet sponge was placed between the clamp and liver; Figure 2); and *(iv)* the deviation group (n=8), in which the two lobes of the liver were deviated cranially as creating angling to vascular structures and sutured to the diaphragm for 30 min (Figure 3). In the deviation group, the sutures were removed after 30 min, and the sutured liver tissue was discarded from the obtained sample tissue.

Experimental protocols

The rats were anesthetized with ketamine hydrochloride (60 mg/kg) and xylazine hydrochloride (7 mg/kg) intraperitoneally,

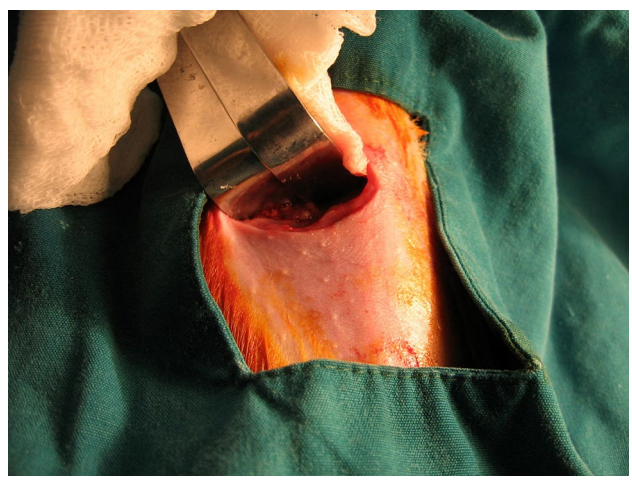

Figure 1. Method used in the retraction group, showing the pressure applied to the liver with Farabeuf's retractor.

and their liver was exposed through a midline abdominal incision in the control, crush, and deviation groups and through a subcostal incision in the retraction group. The liver was traumatized by Farabeuf's retractor in the retraction group (Figure 1), by bulldog clamp in the crush group (one clamp to one lobe; a total of two clamps to two lobes; Figure 2), and by cranial deviation in the deviation group (two lobes of the liver; Figure 3). After 30 min, the traumatizing devices were removed, and a liver tissue sample was taken from one of the traumatized liver lobes in the retraction, crush, and deviation groups and from a healthy lobe in the control group. The tissue sample was divided into two parts: one for pathological examination and one for tissue biochemical examination. The part taken for histological evaluation was placed in 10% neutral buffered formalin solution, and the part taken for tissue biochemical examination was rinsed with isotonic solution, dried, and stored at –80°C. Blood samples of 0.75 mL were collected from the tail vein in all rats at the following time points: before opening the abdominal cavity (preoperative), 30 min after the operation (postoperative), and on the first day (24 h), second day (48 h) and third day (72 h) after the operation for ALT, AST, and LDH measurements. After the preoperative blood sample was collected, before laparotomy, 5 mL isotonic saline was given subcutaneously for fluid resuscitation. Twenty-eight days later, the animals were sacrificed by ketamine hydrochloride (150 mg/kg) intravenously, and liver lobes (normal lobe in the control group and the ones previously traumatized in retraction, crush, and deviation groups) were removed and divided into two parts for histological and biochemical examinations.

Figure 2. Method used in the crush group, showing the liver crushed with a bulldog clamp.

The retraction weight calculation for the retraction group was as follows: the pressure of the bulldog clamp was measured with a device and found to be 1088 kg/m^2 (1.088 g/mm^2; Figure 4). The surface area of the Farabeuf's retractor was calculated as 190 mm^2. Multiplying the bulldog clamp pressure by the surface area of the Farabeuf's retractor resulted in a weight of 207 g. In a preliminary study, 200 g weights were

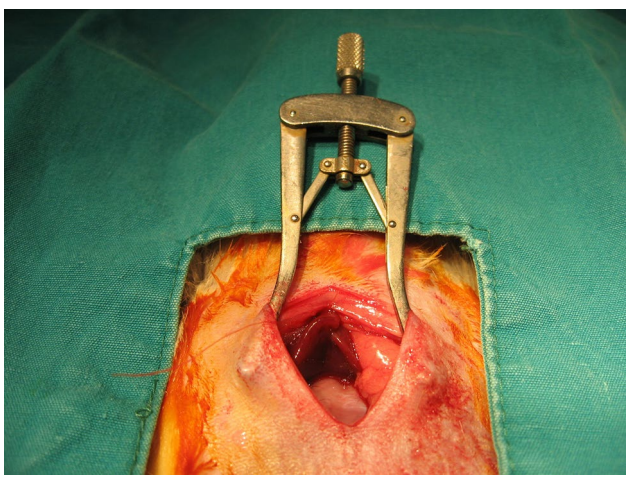

Figure 3. Method used in the deviation group, showing the liver deviated cranially and sutured to the diaphragm.

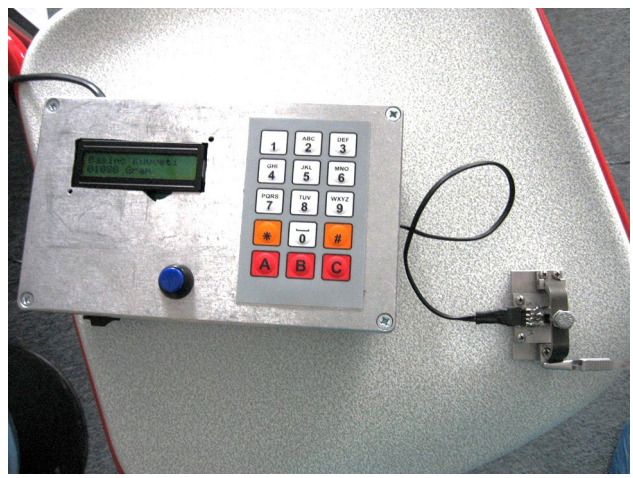

Figure 4. Measurement of pressure applied by the bulldog clamp.

used in the retraction group. However, because the animal's respiration was negatively affected and its body began to move freely from the restraints, the weight was gradually reduced. Finally, with a 100 g weight, it was observed that both the animal's respiration was normal and the animal's body structure remained unchanged with the restraints. Therefore, the 100 g weight was applied to the retraction group (Figure 5).

In the deviation group, two lobes were selected based on rat anatomy to provide the same angle of retraction as in human surgery, and which could be attached to the diaphragm without damaging the other lobes or structures with sutures. The retraction was performed using sutures. The same two lobes were also used in the bulldog clamp crush group, but in the retraction group, the entire liver structure was placed under the retractors. The same lobe was removed in each group for short-term histopathology, and the other (same) lobe was removed in each group for long-term histopathology.

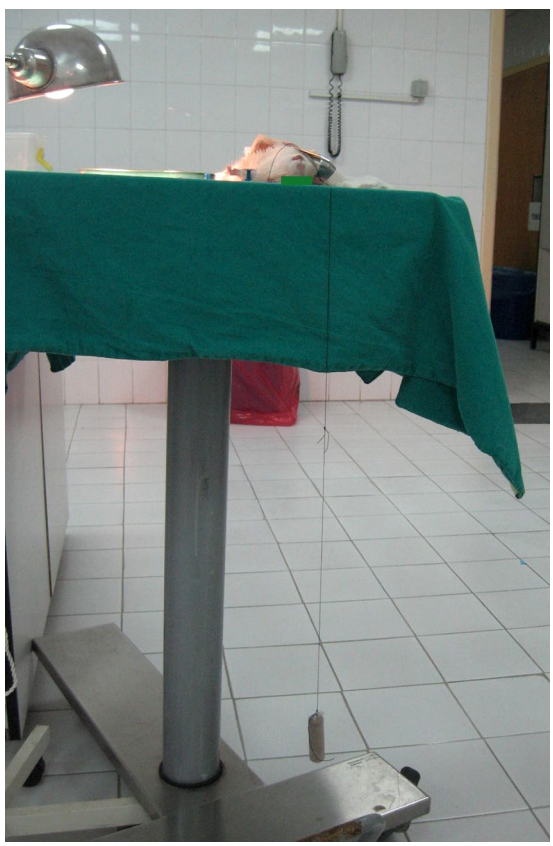

Figure 5. Application of weight to the retractors.

Tissue biochemical measurements

Malondialdehyde (MDA) is a toxic end product of the disintegration of nonenzymatic oxidative lipid peroxidation products. The level of MDA increases in the presence of oxygen radicals, causing cell injury. In many studies, MDA has been used as a parameter to determine tissue injury.[17,18]

Glutathione (GSH) is a tripeptide consisting of glutamic acid, cysteine, and glycine and is more concentrated in the intracellular fluid. It is important as a reducing agent and an antioxidant, protecting cells from the harmful effects of endogenous and exogenous oxidants by maintaining cellular oxidation-reduction balance.[19] Glutathione facilitates the chemical clearance of these radicals by reacting with oxygen radicals; thus, GSH decreases when oxygen radicals increase. As a result, GSH has been used in many studies as a parameter to determine injury caused by oxygen radicals.[17,18]

Hydroxyproline (Hyp) is an important intermediate product in collagen metabolism. The Hyp level determines the severity of cirrhosis and hepatic fibrosis.[20,21]

Determination of tissue MDA and GSH concentrations:

Liver homogenates were prepared in ice-cold 0.15 M potassium chloride (10%, w/v) using an all-glass homogenizer.

Malondialdehyde, as a marker of lipid peroxidation, was determined according to the thiobarbituric acid reaction described by Buege and Aust.[22] One sample volume was combined with two reagent volumes containing 15% trichloroacetic acid, 0.375% thiobarbituric acid, and 0.25 M hydrochloric acid. The mixture was kept in a boiling water bath for 15 min and centrifuged at 1000× g for 10 min after cooling. The absorbance was measured at 535 nm against a reagent blank. Quantitations were obtained using the molar extinction coefficient of 1.56×10^5 $M^{-1}\cdot cm^{-1}$, and the results were expressed as nmol MDA per gram of tissue.

Glutathione levels were assayed in tissue homogenates according to the method of Ellman.[23] After deproteinization of the samples, the Ellman color reagent was added to the supernatant, and

the absorbance of the generated color complex was detected immediately at 412 nm against a reagent blank. Concentrations were calculated by using the GSH calibration curve, and the results were expressed as nmol GSH per gram of tissue.

Determination of tissue Hyp concentrations

Liver homogenates were prepared in ice-cold saline (2 g/5 mL, w/v) using an all-glass homogenizer.

Hyproxyproline levels were assayed in tissue homogenates according to the method of Reddy and Enwemeka.[24] Homogenates and Hyp standards were hydrolyzed in an alkaline medium (2N sodium hydroxide). After neutralization, samples were oxidized with chloramine-T, and the absorbance of the generated color complex with the Ehrlich reagent was detected immediately at 563 nm against a reagent blank. Concentrations were calculated using the Hyp calibration curve, and results were expressed as Hyp per gram of tissue.

Histopathological examination

Tissue samples taken were fixed in 10% formalin, embedded in paraffin, and stained by hematoxylin and eosin. All biopsies were investigated by the same pathologist, who was blinded for the groups. All specimens were examined and graded according to balloon cell degeneration, steatosis, single cell necrosis, centrilobular necrosis, necroinflammatory focus, widespread necrosis, sinusoidal dilatation/congestion, atrophy of hepatocytes, and cholestasis.

Data on single cell necrosis, centrilobular necrosis, necroinflammatory focus, and diffuse necrosis were scored according to their significance as indicators of necrosis and used to create a traumatized liver necrosis score (TLNS; Table 1). The TLNS was used to evaluate acute phase liver tissue injury. Data on necroinflammatory focus, diffuse necrosis, sinusoidal dilatation/congestion, and atrophy of hepatocytes were scored as indicators of long-term tissue damage and used to create traumatized liver permanent damage score (TLPDS) according to their significance. The TLPDS was used to evaluate long-term liver tissue injury.

Statistical analysis

Data were analyzed using IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Definitive values were expressed as median (min-max). For comparing independent groups, the Kruskal-Wallis test was used. When a difference was found, the multiple comparison test of Conover was used to define the group causing the difference. For categorical variables, the chi-square test was used. For repeated measures, analysis of variance for repeated measures and the Bonferroni test were used to compare repeated measures over time. We performed the Mann-Whitney U test for nonparametric and Student's t-test for parametric continuous variables. A p-value <0.05 was considered statistically significant.

RESULTS

One of the rats from the crush group was lost during the operation, and one each from the retraction and deviation groups was lost during the follow-up.

When serum biochemical investigations were evaluated, in all groups, AST and ALT increased at the 30th min and 24th h (for AST p=0.05, p<0.01, respectively; for ALT p=0.02, p<0.01, respectively) and decreased at the 48th h and 72nd h (for AST p=0.05, p=0.02, respectively; for ALT p=0.02, p<0.01, respectively). In all groups, AST and ALT values at the 72nd h were in between the values at the 30th min and the values at the 24th h (for AST p=0.231, p=1.000, respectively; for ALT p=0.418, p=0.432, respectively). In all groups, LDH first increased at the 30th min and decreased afterward. However, the increase at the 30th min and decrease at the 24th h was not significant (p=1.00 and p=0.252, respectively), but the decrease at the 48th h and 72nd h was significant (p<0.01 and p<0.01, respectively) compared to the first measurement. The results are given in Table 2. At postoperative 30th min, ALT and AST levels were higher in the crush group (p=0.004 and p=0.005, respectively), and ALT level was higher in the deviation group (p=0.030) compared to the control group. The LDH levels at the 48th h was significantly higher in the crush group compared to other groups (p=0.020; Table 2).

When tissue biochemical investigations were considered, MDA and Hyp did not differ significantly between groups at postoperative 30 min (p=0.200 and p=0.054, respectively) or on the 28th day (p=0.999 and p=0.152, respectively). In

TABLE 1
Scoring methods used in the study

	Traumatized liver necrosis score (TLNS)		Traumatized liver permanent damage score (TLPDS)	
Single cell necrosis	Absent	0		
	Present (few)	1		
	Present (many)	2		
Centrilobular necrosis	Absent	0		
	Present (focal)	1		
	Present (diffuse)	2		
Necroinflammatory focus	Absent	0	Absent	0
	Present (sparse)	1	Present (sparse)	1
	Present (diffuse)	2	Present (diffuse)	2
Widespread necrosis	Absent	0	Absent	0
	Present (sparse)	2	Present (sparse)	1
	Present (diffuse)	4	Present (diffuse)	2
Sinusoidal dilatation/congestion			Absent	0
			Present (fokal)	1
			Present (mild)	2
			Present (moderate)	3
			Present (severe)	4
Atrophy of hepatocytes			Absent	0
			Present	2
Score		0-10		0-10

the crush group, MDA was higher (p=0.052) and GSH was lower (p=0.064) than the control group at postoperative 30 min, whereas the difference disappeared on the 28th day (p=0.410 and p=0.691, respectively; Table 2).

When the histopathological examination was considered, no steatosis, atrophy of hepatocytes, or cholestasis was observed in any of the groups at any time. The findings of the histopathological examination are given in Table 3.

When the histopathological examination was compared statistically between groups, only postoperative necroinflammatory focus and sinusoidal dilatation/congestion showed significant differences (p=0.048 and p<0.001, respectively; Table 3). All three experimental groups (retraction, crush, and deviation) showed prominent balloon cell degeneration on the 28th day, although the difference was not significant (p=0.092).

Concerning necroinflammatory focus, the retraction, crush, and deviation groups differed compared to the control group (p<0.001) but did not differ amongst themselves. Concerning sinusoidal dilatation/congestion, there were differences between all groups; however, there was no difference in examinations on the 28th day (p=0.207; Table 3).

TABLE 2

Serum and tissue biochemical results and scores according to groups

	Group 1			Group 2			Group 1 *vs.* 2	Group 3			Group 1 *vs.* 3	Group 4			Group 1 *vs.* 4
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	*p*	Mean±SD	Median	Min-Max	*p*	Mean±SD	Median	Min-Max	*p*
ALT (U/L)															
Preoperative	39.8±12.7			90.2±60.4			0.218	46.7±11.9			0.457	75.2±74.8			0.704
Postoperative (30 min)	44.7±15.1			136.2±152.4			0.105	301.7±180.9			**0.004**	123.4±78.1			**0.030**
After 24 h	575.2±261.6			703.2±264.9			0.500	1173.9±786.2			0.801	923.5±538.1			0.900
After 48 h	632.3±500.0			194.6±65.9			0.093	508.3±268.4			0.886	200.0±50.6			0.121
After 72 h	85.8±18.2			83.8±23.0			0.858	93.6±45.8			0.712	101.5±46.0			0.449
AST (U/L)															
Preoperative	86.5±32.0			160.4±94.2			0.688	115.3±36.7			0.416	138.1±112.2			0.982
Postoperative (30 min)	129.8±59.0			228.0±267.6			0.502	358.1±140.4			**0.005**	149.4±79.9			0.745
After 24 h	777.2±291.1			892.9±438.4			0.622	1374.0±1004.1			0.617	1260.5±489.5			0.548
After 48 h	805.2±598.7			302.8±136.9			0.093	797.4±498.7			0.775	344.0±125.1			0.245
After 72 h	173.5±101.6			173.1±57.3			0.993	182.0±82.2			0.821	218.1±105.0			0.441
LDH (U/L)															
Preoperative	1415.8±1296.4			1601.6±1076.2			0.105	2251.9±1439.1			0.343	1653.0±843.9			0.095
Postoperative (30 min)	2789.8±3046.6			1297.8±1408.5			0.181	3901.3±2022.3			0.433	1150.7±826.6			0.102
After 24 h	1458.8±730.1			765.9±383.1			**0.028**	2159.0±2218.5			0.696	1105.4±457.5			0.175
After 48 h	567.8±196.8			402.0±144.6			0.093	1292.4±610.9			**0.020**	536.7±382.6			0.723
After 72 h	711.5±312.8			634.2±347.0			0.675	438.4±434.1			0.240	285.9±11.3			0.018
MDA (nmol MDA/g)															
Postoperative 30 min	28.7±8.6			29.5±8.5			0.888	49.2±26.8			0.052	32.8±8.5			0.287
On 28th day	21.6±6.6			20.1±4.8			0.628	19.8±2.7			0.410	19.7±2.7			0.516
GSH (nmol GSH/g)															
Postoperative 30 min	3.6±1.6			3.9±1.6			0.366	1.6±1.1			0.064	2.4±0.4			0.293
On 28th day	5.0±1.2			5.6±0.8			0.324	4.8±1.0			0.691	5.2±0.9			0.685
Hyp (gHyp/g)															
Postoperative 30 min	65.8±43.7			67.9±26.1			0.805	51.4±9.7			0.213	69.3±10.4			0.696
On 28th day	91.4±21.1			68.6±18.3			0.051	75.1±10.7			0.117	84.5±15.4			0.505
TLNS (Postoperative 30 min)		0	0-0		1	0-2	**0.014**		1	0-2	**0.040**		1	0-4	**0.014**
TLPDS (On 28th day)		0.5	0-3		1	0-3	0.445		1.5	1-4	0.108		2	1-4	0.073

SD: Standard deviation; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; MDA: Malondialdehyde; GSH: Glutathione; Hyp: Hydroxyproline; TLNS: Traumatized liver necrosis score; TLPDS: Traumatized liver permanent damage score. Important ratios with statistical significance are shown in bold.

TABLE 3
Histopathological examination of liver tissue samples taken at postoperative 30 min and on the 28th day

	Postoperative					28th day				
	Group 1 (n=6)	Group 2 (n=7)	Group 3 (n=7)	Group 4 (n=7)		Group 1 (n=6)	Group 2 (n=7)	Group 3 (n=7)	Group 4 (n=7)	
	%	%	%	%	*p*	%	%	%	%	*p*
Balloon cell degeneration										
Absent	83	62	100	75	0.274	83	14	14	14	0.092
Mild	17	38	0	25		17	57	57	43	
Medium	0	0	0	0		0	14	29	14	
Severe	0	0	0	0		0	14	0	29	
Single cell necrosis										
Absent	100	100	100	88	0.572	100	100	100	100	
Present	0	0	0	12		0	0	0	0	
Centrilobular necrosis										
Absent	100	100	100	75	0.105	100	100	100	86	0.375
Present	0	0	0	25		0	0	0	14	
Necroinflammatory focus										
Absent	**100**	**62**	**43**	**38**	**0.048**	50	71	14	43	0.141
Present	**0**	**38**	**57**	**62**		50	29	86	57	
Necrosis										
Absent	100	75	100	75	0.230	83	71	100	86	0.470
Focal	0	25	0	25		17	29	0	14	
Sinusoidal dilatation/congestion										
Absent	**50**	**0**	**0**	**0**	**0.000**	83	29	43	14	0.207
Focal	**33**	**38**	**0**	**0**		17	57	29	43	
Mild	**0**	**12**	**0**	**25**		0	14	14	43	
Medium	**17**	**50**	**14**	**63**		0	0	14	0	
Sever	**0**	**0**	**86**	**12**		0	0	0	0	

Important ratios with statistical significance are shown in bold.

When TLNS scores were examined, the scores of the groups (Group 1 *vs.* Group 2 [p=0.014], Group 1 *vs.* Group 3 [p=0.040] and Group 1 *vs.* Group 4 [p=0.014]) were found to be significantly higher than the control group (Table 2). When TLPDS scores were examined, the scores the experimental groups were not found to be significantly higher than the control group (p=0.445, p=0.108, and p=0.073, respectively; Table 2).

DISCUSSION

Yassa and Peters[16] detected liver trauma after the use of a hepatic retractor during gastric malignancy resections. Their study examined preoperative and postoperative computed tomography scans of 250 patients. They determined lesions with the same findings as those after blunt abdominal trauma in the left lobe of the liver in 10 patients and increased liver enzymes. The authors concluded that hepatic retraction during gastric resection led to hepatic trauma in these patients. Similarly, Kinjo et al.[5] reported that one of their patients had hepatic infarction after laparoscopic gastrectomy in which a Nathanson liver retractor had been used. We also observed an increase in liver enzymes (AST and ALT) in our patients who underwent gastric or biliary system operations.

In our study, serum biochemical analysis showed that serum ALT levels in the crush and deviation

groups significantly increased after the operation compared to the control group, indicating hepatic injury. The serum AST levels also increased in the crush group. Similar to other studies, the difference within groups disappeared at 72 h when all the levels decreased to near-normal levels.[12,14,15]

Some clinical studies have shown that liver enzymes (AST and ALT) increased after both laparoscopic and open upper abdominal surgeries (e.g., gastrectomy, cholecystectomy, antireflux surgery, and obesity surgery), while they did not change after lower abdominal surgeries (e.g., inguinal hernia repair)[5,12,14,25] or after other surgeries out of the abdominal region (e.g., head and neck, breast, thorax, and testis).[3,4] Most of these studies concluded that liver retraction is the cause of the increase in liver enzymes,[3-5,12,14] and some authors added the effects of anesthetic drugs.[12] However, some authors concentrated on the effects of position (head up position during laparoscopy) and pneumoperitoneum.[25]

Saranita et al.[26] showed that their patient with an open Roux-en-Y gastric bypass had increased liver enzymes after the hepatic retractor was placed. Additionally, some studies were conducted to define which type of liver retraction was less harmful to the liver tissue.[6] When we look at all these studies in the literature, it is observed that liver retraction increases liver enzymes, the increase of which is an indicator of liver damage.

It is known that when tissue injury is present, tissue MDA and Hyp levels increase, and GSH levels decrease. Levels of MDA and GSH in the liver tissue were measured to demonstrate tissue injury, and Hyp levels in the liver tissue were measured to demonstrate fibrosis. When tissue biochemical analyses of our study were examined, the only significant difference was the increase in MDA and the decrease in GSH in the crush group, indicating mild oxidative injury, although the differences were not statistically significant. The changes in MDA and GSH in the crush group showed recovery on the 28th day. The crush group also showed a significant increase in serum ALT and AST levels postoperatively and serum LDH levels on the second day, indicating that the intervention in the crush group caused hepatic injury more prominently.

The postoperative presence of necroinflammatory focus showed statistical significance in the retraction, crush, and deviation groups compared to the control group. Necroinflammatory focus is a tissue injury finding; however, it is nonspecific.

Postoperative presence of sinusoidal dilatation/congestion showed statistical significance within groups. Interestingly, postoperatively, the most severe sinusoidal dilatation/congestion was observed in the crush group. This could be due to the compression of venules by the applied pressure, impairing venous return and causing congestion. Furthermore, the deviation group showed mostly medium congestion postoperatively, which was thought to be due to the angulation of veins, causing venous stasis. Congestion in the retraction group was not as severe as in the crush group and significantly more than in the control group. As congestion was significant, and cholestasis was not observed, we can say that the bile ductile is more resistant to compression and pressure trauma than hepatic venules.

For all groups, although the necroinflammatory focus and sinusoidal dilatation/congestion did not recover on the 28th day, the severity decreased, and the difference within the groups disappeared. However, balloon cell degeneration, a finding of hepatocyte death and apoptosis, became more evident on the 28th day. This shows that all three mechanisms may cause hepatocyte apoptosis in the long term.

Necrosis was the most important finding for tissue injury. Although it was only observed in the retraction and deviation groups at postoperative 30 min, statistical analysis showed no significant difference between the four groups. Interestingly, necrosis was not observed in the crush group at postoperative 30 min or on the 28th day, although a significant increase in serum ALT, AST, and LDH levels, an increase in tissue MDA levels, and a decrease in tissue GSH levels were observed, indicating tissue injury.

This study used the TLNS and TLPDS scoring systems for the first time. The TLNS is a combination of parameters that indicate necrosis and showed a significant difference between the control group and the retractor, crush, and deviation groups, indicating that retraction and its components caused significant necrosis of the

liver tissue. The TLPDS showed no significant difference between the control and experimental groups, indicating that permanent damage was not significant.

These findings can also enlighten the pathology of blunt hepatic trauma, as a similar mechanism with crush injury appears to happen at blunt trauma hepatic injury.

No study was found in the literature that could be compared with our study regarding damage to the liver caused by liver retraction or blunt liver trauma. Our findings indicate that liver retraction causes mild acute damage to the liver tissue, which causes balloon cell degeneration, a finding of hepatocyte death and apoptosis in the long term and increased necrosis parameters. Although this mild damage is insignificant in normal liver tissue, it may be significant in patients with critical or borderline liver reserve, such as the liver tissue of patients with cirrhotic liver or biliary atresia. We found that the crush mechanism was more harmful to the liver tissue than the angling of vascular structures for a short time. Therefore, we recommend that surgeons maintain hepatic retractions at minimum tension during surgical procedures to protect the liver tissue, particularly in biliary atresia surgeries and cirrhotic cases.

This study had some limitations. The sample size was small. As no previous study was designed for this topic, we did not have data to calculate the sample size of groups during the planning stage of the study. However, the results could be more precise if the sample size was larger. Second, we could not find a way to equalize retraction pressure and crush pressure applied by bulldog clamps. Crush pressure may be more than retraction pressure in this study. Third, the hepatic enzymes increased in all groups, including the control group, which may be due to anesthetic drugs, making comparisons more difficult. Lastly, as we could not find any study discussing hepatic damage or histopathological changes due to retraction, the discussion and comparison of our results with the literature were limited.

In conclusion, while the crush group showed significant injury, with an elevation of serum ALT, AST, and LDH levels, an increase in tissue MDA levels, a decrease in tissue GSH levels, severe sinusoidal dilatation/congestion, and the presence of a necroinflammatory focus in the postoperative histopathological findings, the retraction and deviation groups showed signs of hepatic injury only by the postoperative presence of sinusoidal dilatation/congestion and necroinflammatory focus. According to the histopathological findings, although balloon cell degeneration, sinusoidal dilatation/congestion, and necroinflammatory focus were still observed on the 28th day in the retraction, crush, and deviation groups, statistical analysis did not reach the level of significance. These findings show that the crush mechanism was more harmful to the liver tissue than the angling of vascular structures for a short tiâdue to liver retraction, and the effects of the damage were evident in the long term.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Material preparation, data collection, processing and analysis were performed: T.A.D., N.A.H.R., D.A.A.; Literature review was done: T.A.D., D.A.A.; The first draft of the manuscript was written: T.A.D., N.A.H.R.; Made critical review of the manuscript: D.A.A. All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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