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HYPERTONIC SALINE DEXTRAN ALLEVIATES HEPATIC INJURY IN HYPOVOLEMIC RATS UNDERGOING PORTA HEPATIS OCCLUSION

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ABSTRACT—To monitor the ischemic and/or reperfusion injury after porta hepatis occlusion (Pringle maneuver) in livers subjected to hypotension, serum alanine amino transferase (ALT), liver malondialdehyde (MDA), and liver glutathione (GSH) levels were measured. MDA is a by-product of oxidant-induced lipid peroxidation, and GSH is an endogenous antioxidant. The effects of lactated Ringer's (LR) and hypertonic saline (7.5%)/Dextran (6%; HSD) resuscitation on liver injury, if any, was investigated. Rats in sham (S, n = 8) and five other groups (n = 8) underwent femoral artery and vein catheterization and laparotomy. The hemorrhage and ischemia (HI) group was bled 30% of their blood volume and had their porta hepatis occluded for 30 min. The HI, LR, and HSD groups underwent both hemorrhage and occlusion. Thirty minutes after hemorrhage, the LR and HSD groups received either LR (equivalent to three times the shed blood) or HSD (10 mL/kg) resuscitation over 30 min. Both LR and HSD resuscitation lowered the increased ALT and liver tissue MDA seen in the HI group. ALT was decreased from 348 ± 93 IU/L in the HI group to 200 ± 98 IU/L in the LR and 139 ± 74 IU/L in the HSD groups. Liver tissue MDA was 353 ± 22 nmol/g/tissue in the HI group and LR decreased it to 261 ± 17 nmol/g/tissue, whereas HSD decreased it to 273 ± 20 nmol/g/tissue. The decrease in ALT and the increase in liver GSH were more pronounced with HSD resuscitation ($P < 0.05$). HSD seems to be more effective than LR in decreasing the liver tissue damage produced by total hepatic inflow occlusion under hypovolemic conditions.

KEYWORDS—Ischemia-reperfusion, hypovolemic shock, hypertonic saline Dextran, lactated Ringer's

INTRODUCTION

Hypovolemic shock usually accompanies major liver trauma, and, in the surgical management of these patients, transient portal occlusion (Pringle maneuver) is frequently used. Under normovolemic conditions, the sensitivity of liver tissue to warm ischemia increases with the length of the ischemic period. Studies have shown that ischemic periods longer than 30 min may cause serious liver injury (1–3). Liver tissue has the highest population of macrophages in the body and therefore has great potential for the production of local and/or systemic inflammatory response. Several other studies have indicated that both hepatic ischemia and hemorrhagic shock can activate Kupffer cells and increase cytokine release (4–6). Hemorrhagic shock and resuscitation can be considered an ischemia and reperfusion phenomenon of the entire organism in which cytokines are released and reactive oxygen metabolites (ROM) are increased (7, 8). Increased ROM production causes lipid peroxidation of the cell membranes, activation of the neutrophils, and release of more cytokines. Both cytokine and ROM release play significant roles in the production of a systemic inflammatory response, which, in turn, may cause local and/or distant organ injury.

The tolerance of the already hypoperfused liver, as in hypovolemic shock, to an ischemic insult such as the Pringle maneuver, has not yet been investigated. The prevention of this liver injury in hypotensive patients with major hepatic trauma may be beneficial in the reduction of postoperative morbidity and mortality. Hypertonic saline (7.5%) and Dextran(6%; HSD) is a small-volume resuscitation fluid with antioxidant properties. HSD is said to improve microcirculation and decrease reperfusion injury by scavenging ROMs in shock (9). Resuscitation fluids other than HSD with antioxidant properties have been shown to decrease the hemorrhagic shock-induced leukocyte adhesion in the liver (10). In the literature, there are many studies investigating the effects of HSD as a resuscitation fluid, but the effects of HSD on ischemia and reperfusion injury of the hypoperfused liver have not been investigated.

In clinical practice, hemorrhagic shock is usually not an isolated finding, but instead is frequently accompanied by other organ injuries. Separately, transient hypovolemic shock and transient liver ischemia may be tolerated well by the organism, but if these two processes occur at the same time, the combined effect may cause serious liver and/or distant organ injuries. Thus far in the literature, we were not able to find a study investigating the effects of rapid small-volume resuscitation in a model of systemic hypovolemia followed by liver ischemia. In this study, we hypothesized that HSD resuscitation will decrease the hepatocellular damage in hypovolemic rats undergoing porta hepatic occlusion.

MATERIALS AND METHODS

Animal preparation

Thirty-two male Sprague-Dawley rats, weighing 250–350 g, were used with institutional approval from the Uludag University Animal Care and Use Committee. Our institution's guide for the care and use of laboratory animals was strictly followed. The animals were housed in a room with controlled temperature (24°C) and were starved for 12 h before the experiments. Thiopental sodium (Pentothal Sodium®, 40 mg/kg; Abbott, Istanbul, Turkey) was used intraperitoneally for anesthesia. Throughout the experiments, body temperature was kept at 36°C to 38°C.

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The rats were placed in the supine position, the right groin was shaved, and a rectal temperature probe was placed. Polyethylene cannulas were inserted into the femoral artery for blood pressure monitoring, blood sampling, and to bleed the animals, into the femoral vein for administration of resuscitation fluids. A multichannel polygraph (Propoq104; Protocol Systems, Beaverton, OR) was used to monitor heart rate, systolic blood pressure (SBP), and temperature during the experiment. HSD was prepared in our laboratory by the addition of 6% Dextran (Eczacibasi-Baxter, Istanbul, Turkey) to 7.5% hypertonic saline (NaCl) solution.

Study groups

Thirty-two rats were randomized into four groups (n = 8). A sham (S) group underwent arterial and venous cannulation and laparotomy. The hemorrhage and ischemia group (HI) was bled 30% of their blood volume and had their porta hepatis occluded for 30 min, but did not receive fluid resuscitation. The lactated Ringer's (LR) and HSD groups underwent both hemorrhage and porta hepatis occlusion. The LR group received LR resuscitation for 30 min, and the HSD group received HSD resuscitation for 5 min after hemorrhage. The experimental design of study is shown in Figure 1.

Hemorrhagic shock

Animals were bled, over 5 min, 30% of their total blood volume (Class 3 shock) via the arterial cannula 10 min after catheter insertion. This volume was estimated by multiplying 5% of the rat's weight by 30%. The shed blood withdrawn through the cannula was measured for each rat. The rats were then left hypovolemic for 30 min, and no further bleeding or resuscitation was used during this time period.

Resuscitation

At the end of the 30-min hypovolemic period, fluid resuscitation was started. Animals in the LR group were resuscitated for 30 min with LR (equivalent to three times the shed blood) by an infusion pump. The HSD group received 10 mL/kg HSD resuscitation for 5 min. Thirty minutes after the beginning of the fluid resuscitation, animals in both groups received 1 mL/kg/h LR intravenously to maintain hemodynamic stability throughout the study period.

Hepatic ischemia

At the end of the 30-min hypovolemic period, concomitant with the start of fluid resuscitation, a midline laparotomy was performed in approximately 3–5 min, and the liver hilum was exposed. In all groups except the sham group, the entire hepatic pedicle was occluded for 30 min with a bulldog clamp.

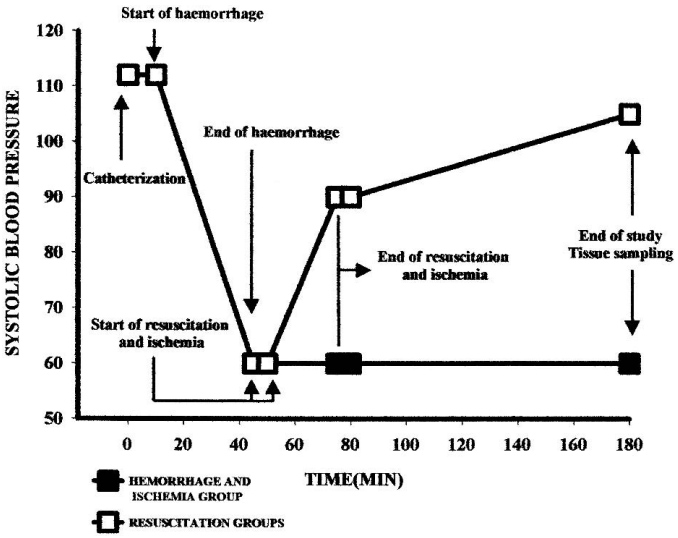

FIG. 1. **Experimental design for the study.** There were four groups of animals with eight rats in each group. Time is on the *x* axis. Rats were bled, over 5 min, 30% of their blood volume 10 min after catheterization. At the end of the 30-min hypovolemic period, concomitant with the start of fluid resuscitation, a midline laparotomy was performed in approximately 3–5 min, and the liver hilum was exposed. In all groups except the sham group, entire hepatic pedicle was occluded for 30 min with a bulldog clamp. The hemorrhage and ischemia group did not receive fluid resuscitation. Fluid resuscitation was at the end of this 30-min shock period with either LR or HSD. The LR group received LR resuscitation for 30 min, and the HSD group received HSD resuscitation for 5 min after hemorrhage.

Blood and tissue sampling

At the end of 180 min, blood samples were taken from the femoral artery to measure the serum alanine aminotransferase (ALT) levels, and biopsy specimens were taken from the right lobe of the liver to measure levels of hepatic glutathione (GSH) and malondialdehyde (MDA).

Biochemical analysis

At the end of 3 h, all rats were sacrificed by drawing their total blood volume from the femoral artery. The livers were harvested, washed in cold saline, dried on filter paper, and stored at −40°C for subsequent analysis. All biochemical assays were performed within 4 days of sample freezing. The MDA levels were measured as thiobarbituric acid reactive substances (TBARS) in tissues according to the calorimetric methods of Kamal et al. (11) and Okawa et al. (12), respectively, and are presented as nanomoles MDA either per milliliter or per gram of tissue. The values are reported as the optical density (OD) reading at 532 nm. Hepatic tissue samples were assayed for reduced GSH according to the method of Sedlak et al. (13). This method spectrophotometrically determines the levels of sulfhydryl groups in tissue. Samples were weighed and homogenized by 5,5-dithiobis-2-nitrobenzoic acid (DTNB). The rate of formation of 5-thio-2-nitrobenzoic acid (TNB) was monitored at 412 nm in a spectrophotometer. The values were expressed as micromoles per gram of tissue. Levels of ALT were measured using automated laboratory analyzers (Johnson and Johnson Clinical Diagnostic, Rochester, NY) and are expressed as international units per liter.

Statistical analysis

All values presented in the text and figures are expressed as the mean ± SD. A statistical analysis was performed using Kruskal-Wallis nonparametric test and Mann-Whitney *U* test for determining the differences between the groups. Statistical significance was accepted if $P < 0.05$.

RESULTS

There were no differences among the groups as far as the weights of the rats were concerned. Six rats were removed from the study, two due to death during arterial cannulation and four due to death during the hypovolemic period. Deaths in the hypovolemic period were as follows: two from the HI, one from the LR, and one from the HSD groups.

Blood pressure results

Initial SBPs were similar among all the groups. At the end of the study, SBP was 62 ± 6.9 mmHg in the HI group, 106 ± 8.5 mmHg in the LR group, and 105 ± 7.6 mmHg in the HSD group. SBP was significantly lower in the HI group when compared with either the LR or the HSD groups. No significant difference was found in the SBP between the LR and HSD groups. Figure 2 shows the percentage change from baseline of the SBP in each group.

Liver tissue MDA results

Liver tissue MDA results were found to be significantly increased in the HI group (353 ± 22 nmol/g) when compared with the sham group (293 ± 17 nmol/g). Liver tissue MDA was similar in the LR (261 ± 17 nmol/g) and HSD (273 ± 20 nmol/g) groups, but both were significantly lower than the HI group ($P < 0.05$). Liver tissue MDA results are shown in Figure 3.

Liver tissue GSH results

Liver GSH levels were found to be increased significantly only in the HSD group when compared with the other three groups ($P < 0.05$). Results are shown in Figure 4.

ALT results

ALT was significantly high in the HI group (348 ± 93 IU/L) when compared with the sham group (52 ± 7 IU/L). LR resus-

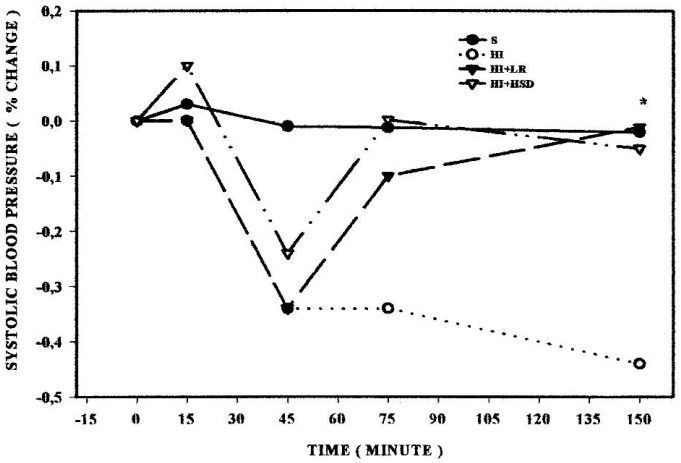

FIG. 2. **SBP over time.** Results are presented as the percentage of change from baseline. SBP was significantly lower in the HI group when compared with the either HI + LR or the HI + HSD groups. No significant difference was found in the SBP between the LR and HSD groups ($P < 0.05$* HI + HSD, HI + LR vs. HI).

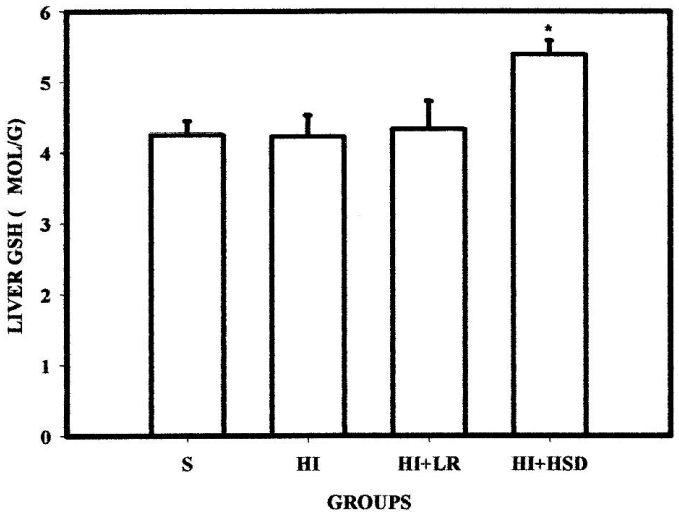

FIG 4. **Liver GSH levels were found to be increased significantly only in the HI + HSD group when compared with the other three groups (**$P <$ 0.05 * HI + HSD vs. S, HI, and HI + LR**).**

citation decreased the ALT levels to 200 ± 98 IU/L, whereas HSD resuscitation decreased it to 139 ± 74 IU/L. The decrease was more significant the HSD group ($P < 0.05$; Fig. 5).

DISCUSSION

The experimental model in this study is somewhat different from other hemorrhagic shock models in the literature. In the literature, blood pressure monitoring is usually done according to mean arterial pressure (MAP). In this study, we chose to use SBP to imitate the clinical setting described as class III shock in the Advanced Trauma Life Support (ATLS) manual (14). The ATLS manual describes class III hypovolemic shock as 30%–40% loss of the total blood volume with a SBP below 80 mmHg and a pulse rate over 120 per min. In this study, rats were bled 30% of their blood volume, which was calculated as 5.3% of their body weight (15).

Fasting may decrease liver GSH levels and rats may adopt their livers to these decreased GSH levels. This adaptation may be considered a preconditioning that increases liver tissue's tolerance to ischemia (7). To prevent any discrepancies among the groups due to different levels of increased tolerance for hypoxia, the 12-h fasting period was strictly observed for each animal.

In this study, we concentrated on detecting the early hepatocellular injury and the effects of HSD on this phenomenon. Studies have shown that the optimal time period for evaluating the inflammatory response of liver to an insult is the first 6 h (16). Hemorrhage and resuscitation is generally accepted as a total ischemia and reperfusion phenomenon for the organism, and postshock tissue injury is largely attributed to ROM (7, 8). The mechanisms involved in liver tissue damage seen after isolated hepatic ischemia and reperfusion are similar to that seen after hemorrhagic shock and resuscitation. Both posthem-

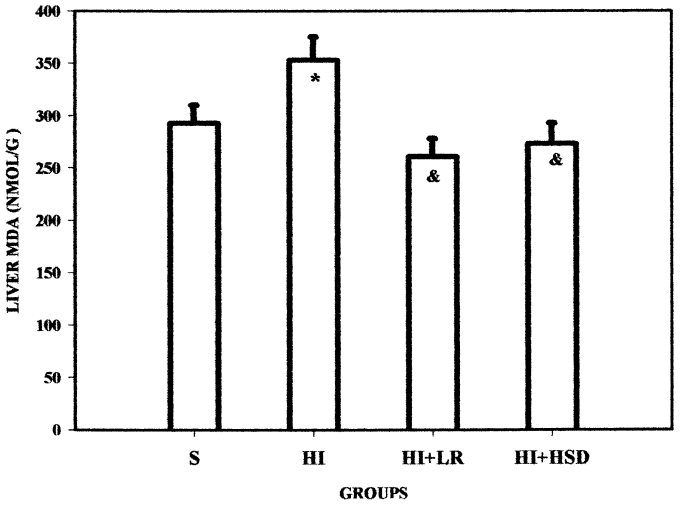

FIG. 3. **Liver tissue MDA results.** Liver tissue MDA results were found to be significantly increased in the HI group when compared with the sham group. Liver tissue MDA was similar in the HI + LR and HI + HSD groups, but both were significantly lower than the HI group ($P < 0.05$ * HI vs. S, and HI + HSD, HI + LR vs. HI).

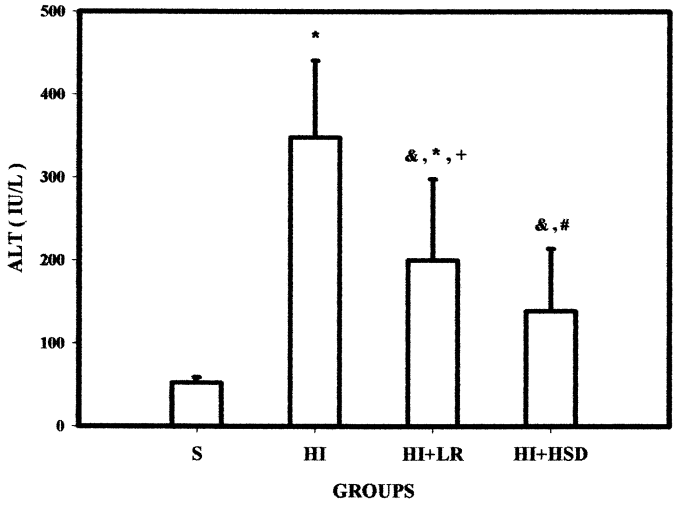

FIG. 5. **Serum ALT results.** Serum ALT increased significantly in the HI group when compared with the S group. LR and HSD resuscitation decreased the ALT levels, but the decrease was more significant in the HSD group ($P < 0.05$ *HI, HI + LR, and HI + HSD vs. S, and HI + LR, HI + HSD vs. HI, #HI + HSD vs. HI + LR).

orrhagic shock and postischemia and reperfusion injury pathophysiological changes in the liver are complex and multifactorial. Some of these changes are increased neutrophil adhesion to the endothelium, nitric oxide (NO) synthetase inhibition, increased TNF-α and IL-1 production, Kupffer cell activation, upregulation of the expression of adhesion molecules (selectins, β_2 integrins, CD11b/CD18, and ICAM-1), and the release of ROM. Recent studies on hepatic ischemia and reperfusion have shown that nuclear factor-κB (NF-κB) increases the expression of messenger RNA that is responsible for the synthesis of inducible NOS, TNF-α, and ICAM-1. Antioxidant N-acetylcystein inhibits NF-κB binding and this finding suggests that NF-κB activation takes place through ROM arising in hepatic ischemia (17–19). TNF-α and IL-1 are the main mediators upregulating the adhesion molecules and thus producing the early inflammatory response. It has been shown that inhibition of P-selectin production in the liver endothelial cells prevents the rolling and adhesion functions of the leukocytes (20). Activation of neutrophils and the Kupffer cells, activation of the xantine oxidase that catalyzes the breakdown of adenosine to xantine and hypoxantine, the production of peroxynitrite from NO, and activation of oxidases such as cytochrome p-450 are the major sources of the ROM (3, 21, 22). In either the isolated ischemia and reperfusion or the hemorrhagic shock and resuscitation setting, these injury-inducing mechanisms appear to act in a rather complex and intermingled way, the net result of which is microvascular damage and tissue injury.

When these physiopathological mechanisms are taken into consideration, in addition to regulation of the microvascular circulation, the prevention of excessive ROM production, regulation of the systemic inflammatory response, and inhibition of neutrophil activation and adhesion must also be important goals of the resuscitation process. In hemorrhagic shock models resuscitated with LR only, neutrophil activation was found to be increased when compared with the controls. This was true even for those rats that received LR infusion without any hemorrhage or shock (23, 24). Deb et al. (25) have investigated the effects of different resuscitation fluids on apoptosis in posthemorrhagic shock rats and have found that intestinal and liver apoptosis is increased with LR resuscitation. Some investigators claim that hypertonic solutions correct hemodynamic parameters better than LR resuscitation and prevent trauma-induced immunosuppression by decreasing neutrophil adhesion (26, 27). Hartl et al. (28) have shown that hypertonic saline (HS) can prevent the early activation of neutrophils after traumatic cerebral injury. Angle et al. (29) reported that HS can decrease posthemorrhagic shock lung injury by suppressing neutrophil activation. These investigators have found out that the increased levels of L-selectin after resuscitation with LR in shock (MAP = 40mmHg) was not encountered with hypertonic saline resuscitation (29). The mechanism of this feature of hypertonic solutions to suppress neutrophil activation has been investigated by others as well. Coimbra et al. (30) state that HS can prevent hemorrhage-induced immunosuppression by decreasing prostaglandin E_2 and interleukin-4 levels. Rizoli et al. (31) indicated that HS decreases the over production of CD11b, an important adhesion molecule on the neutrophil surface. In this study, the authors have shown that hypertonic solutions decrease the neutrophil CD11b expression activated by endotoxin administration (31). All of these studies suggest that hypertonic solutions can improve the microvascular circulation by decreasing neutrophil activation and adhesion and, at the same time and by the same mechanism, decrease oxidative burst and thus overproduction of ROM. The addition of Dextran to hypertonic solutions has been shown to increase the beneficial effects of these solutions on hemodynamic parameters. Dextran also increases tissue perfusion and decreases leukocyte endothelial cell interaction thus preventing adhesion of leukocytes to the endothelium. HSD has been shown to decrease leukocyte accumulation in the sinusoidal and postsinusoidal venules (32, 33). A study done with Dextran alone has indicated that the mechanism of decreased leukocyte-endothelial cell interaction is through Dextran's ability to cover the adhesive structures on the surfaces of the leukocytes, platelets, and endothelial cells. In this study, Dextran's ability to scavenge ROM has also been implicated as a possible mechanisms (34). Corso et al. (9) have shown that HSD resuscitation was able to decrease the early leukocyte accumulation within the liver induced by hemorrhagic shock (9). Other investigators also agree that HSD shows its antioxidant and microcirculatory effects by scavenging ROM and covering the receptors on the endothelial cells and the leukocytes. These investigators state that HSD decreases platelet adhesion and attenuates the platelet-dependent leukocyte-endothelium interaction (35, 36).

The above-mentioned physiological mechanisms may explain the beneficial effects of the HSD resuscitation on hepatocellular damage seen in our study model, but how shall we explain the higher GSH levels in the HI group when compared with the sham group? GSH levels are expected to decrease in hemorrhagic shock. Even preoperative fasting can cause GSH depletion (8). Our explanation for this discrepancy is that we probably missed the early decrease in the liver tissue GSH due to shock and ischemia-reperfusion in our study. The balance between reduced glutathione (GSH) and oxidized glutathione (GSSG) is a dynamic process controlled by tissue oxidant stress. If we had taken our samples right after declamping the porta hepatic when oxidant stress was maximum instead of at the end of the study period, we probably would have found the liver GSH levels lower than the sham group because most of the endogenous GSH supplies would have been consumed. However, GSH was rapidly replaced from the plasma or was resynthesized in the liver tissue itself to overcome this oxidant stress of the liver. According to Robinson et al. (37), in hemorrhagic shock, if the organism is unable to increase its depleted GSH, the risk of organ dysfunction is increased.

In our study, GSH levels were higher, but MDA levels were similar in the HSD group when compared with the LR group. This finding implies that although the rate of lipid peroxidation is similar in both the HSD or LR resuscitations, the beneficial effects of HSD on preventing hepatocellular damage is not solely due to the antioxidant properties of the solution but also to its other features such as optimizing the microcirculation and decreasing tissue edema. Because ALT is an indicator of cellular damage, the elevated GSH levels in the HSD group may be

the reflection of the locally increased production of GSH by the undamaged hepatic cells and not its decreased consumption.

Although they did not find any difference between LR or antioxidant resuscitation as far as GSH depletion seen in hemorrhagic shock was concerned, Yamakawa et al. (38) found that hepatocellular damage, namely ALT, was more favorably influenced by the antioxidant resuscitation rather than the LR resuscitation. Bauer et al. (10) used a different antioxidant resuscitation, hydroxylethyl starch conjugated with deferoxamine (HES-DFO) in hemorrhagic shock. These investigators, too, have found that antioxidant resuscitation decreases hepatocellular damage, and reduces liver glutation depletion and lipid peroxidation. Similarly, Jarrar et al. (39) have reported that the addition of a free radical scavenger, 2-mercaptopropionyl glycine, to the resuscitation fluids can decrease ALT levels and improve posthemorrhagic shock liver injury.

The differences among the above-mentioned studies, including ours, as far as the GSH and MDA levels are concerned probably stem from the different levels of hemorrhagic shock, the presence or absence of a second hit, the antioxidant resuscitation solution used, or the timing of the essays.

In conclusion, our findings suggest that HSD resuscitation decreases liver tissue damage after hemorrhagic shock combined with ischemia and reperfusion of the liver. The exact mechanism of this beneficial effect is still speculative.

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