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Is there any potential or additive effect of anemia on hepatorenal syndrome?

LIVER

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Original Article

ABSTRACT

Background/Aims: Hepatorenal syndrome (HRS) is a severe complication of advanced cirrhosis and is characterized by renal dysfunction and poor survival rates. Although anemia is a non-rare condition in advanced liver cirrhosis, there is no publication regarding the potential or additive effects of anemia on HRS and renal dysfunction in patients with cirrhosis. We investigated whether severe anemia is a precipitant factor for HRS.

Materials and Methods: In this prospective study, consecutive patients with cirrhosis with and without renal dysfunction were enrolled. A total of 29 patients with cirrhosis with HRS meeting the HRS diagnostic criteria (9 patients with type 1 HRS and 20 with type 2 HRS) and 37 patients with cirrhosis without HRS were included. The demographic features, laboratory data (particularly anemic parameters), and clinical scores of patients with and without HRS were evaluated.

Results: Grades of ascites, Child–Turcotte–Pugh (CTP) scores, and Model of End Stage Liver Disease (MELD) scores were significantly higher in contrast to hemoglobin levels; hematocrit concentrations were significantly lower in patients with type 1 and 2 HRS than in those with non-HRS stable cirrhosis. There was a negative correlation between the hemoglobin–hematocrit and serum creatinine levels. In the logistic regression analysis, the hemoglobin levels and CTP and MELD scores were statistically significant for an onset of HRS.

Conclusion: Anemia may contribute to HRS and deteriorated renal function in patients with HRS because anemic hypoxia can lead to microcirculatory renal ischemia in the kidneys and anemia can also activate sympathetic activity and hyperdynamic circulation in the pathogenesis of HRS.

Keywords: Liver cirrhosis, anemia, renal hypoxia, renal dysfunction, hepatorenal syndrome

INTRODUCTION

Hepatorenal syndrome (HRS) is a severe and life-threatening complication of advanced cirrhosis and is characterized by renal dysfunction. Type 1 HRS is characterized by an acute progressive decrease in kidney function and very short survival without treatment, whereas type 2 HRS is characterized by a stable, less severe kidney failure and longer survival than type 1 (1).

The abnormal hemodynamics, which appear to play a role in renal dysfunction in cirrhosis, include portal hypertension, splanchnic and systemic vasodilatation, sympathetic activation, increased cardiac output, hyperdynamic circulation, activated renin–angiotensin–aldosterone system, renal vasoconstriction, and decreased renal perfusion (2-4). These abnormalities are triggered by some vasodilators, such as nitric oxide (NO), in the splanchnic circulation (5,6). Spontane-

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ous bacterial peritonitis, infections, hypotension, overdose of diuretics, large-volume paracentesis, worsening liver function, and variceal bleeding are the precipitant factors of HRS.

Renal ischemia is the most common cause of renal failure. Renal tissue hypoxia can trigger the initial tubular damage. Anemia is a cause of microcirculatory tissue ischemia or hypoxia, which is called anemic hypoxia. Additionally, anemia aggravates sympathetic activation and hyperdynamic circulation in patients with cirrhosis (7,8).

Anemia may occur during liver cirrhosis due to varices, portal hypertensive gastropathy, gastrointestinal erosions and losses, pancytopenia associated with splenomegaly, bone marrow depression from increased levels of proinflammatory cytokines, iron or vitamin deficiencies, and malnutrition. Although anemia is a non-rare condition in advanced cirrhosis, there is no publication addressing the potential or additive effects of anemia on HRS and renal dysfunction in patients with cirrhosis. Therefore, this study aimed at investigating the clinical effects of anemia on renal functions in HRS.

MATERIALS AND METHODS

Study design

This prospective study was performed at the inpatient and outpatient gastroenterohepatology clinics of our university hospital. The local ethics committee approved the study protocol; the study was performed according to the Declaration of Helsinki, following the guidelines for good clinical practice. All patients or their relatives were informed about the study, and informed consent was obtained.

Consecutive patients with cirrhosis with and without renal dysfunction were enrolled in the study between June 2010 and February 2012. These patients had clinical and/or histopathologic diagnosis of cirrhosis secondary to various other causes, including viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, and unknown etiologies. The data collected in this study were also used in another prospective study on neutrophil gelatinase-associated lipocalin in the prediction of mortality in hepatorenal syndrome (9).

Demographic features, routine hemograms, and biochemical and urinary test results were recorded. Estimated glomerular filtration rate (eGFR) was calculated by the 24-hour urine collection method. Child–Turcotte–Pugh (CTP) and Model of End Stage Liver Disease (MELD) scores were calculated. The severity of ascites was detected by abdominal ultrasound evaluation. In addition, a urinary system ultrasound was also performed to exclude the postrenal causes of renal dysfunction.

The exclusion criteria were determined as fluid loss or volume depletion, shock, use of a nephrotoxic agent, infection, proteinuria >500 mg/day, urine red blood cells >50 per high-power field, post-renal pathology, and patients without complete HRS diagnostic criteria. For patients with renal dysfunction (creatinine >1.5 mg/dL), diuretics were stopped at least two days prior and appropriate albumin and/or saline solutions were infused to the patients to exclude the occurrence of prerenal acute kidney injury due to volume depletion (1,10).

All patients were followed in-hospital and out-of-hospital for six months.

Patients groups

According to the results of the evaluation, the patients were divided into three groups.

Type 1 HRS group: These patients had serum creatinine values >2.5 mg/dL and/or a two-fold increase in serum creatinine during a two-week follow-up (11).

Type 2 HRS group: These patients had serum creatinine values >1.5 mg/dL (11).

Group 1 and 2 patients were evaluated and divided according to HRS diagnostic criteria.

Non-HRS group: These were stable patients with cirrhosis without renal dysfunction. These patients had serum creatinine values <1.5 mg/dL.

The severity of cirrhosis was not considered as a determining factor for these groups. The main determining factor for the distribution of the patients into these groups was serum creatinine.

Statistical analysis

The data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 21 (SPSS Inc.; Chicago, IL, USA). Values were presented as mean±standard deviation. The analysis of the binary group of normally distributed variables was evaluated by independent t-test. The multi-group variance analysis was determined by one-way ANOVA. Post-hoc Bonferroni analysis was used for intergroup comparisons. Pearson's correlation analysis was used for correlation analysis. Logistic regression analysis was performed for introduction to HRS. The value of $p \leq 0.05$ was accepted as statistically significant.

RESULTS

A total of 66 patients (9 with type 1 HRS; 20 with type 2 HRS; and 37 without HRS) with cirrhosis were included in the study.

A total of 118 consecutive patients with cirrhosis with serum creatinine ≥1.5 mg/dL were screened and evaluated in terms of the presence of HRS. Sixty-seven patients were diagnosed with prerenal azotemia due to volume depletion. 22 patients had suspicious nephrotoxic drug use and intrinsic causes as

the cause of their renal dysfunction. Consequently, 29 patients fulfilled the criteria for HRS.

For the patients who were included in the study, the following etiologies of liver disease were present: hepatitis B in 29 patients (43.9%), hepatitis C in 9 patients (13.6%), primary biliary cirrhosis in 4 patients (6.0%), nonalcoholic steatohepatitis in 3 patients (4.54%), alcoholic liver disease in 2 patients (3.0%), autoimmune hepatitis in 2 patients (3.0%), and cryptogenic cirrhosis in 17 patients (25.7%). Among all patients with cirrhosis (HRS and non-HRS), eight were in the CTP-A stage, 18 were in the CTP-B stage, and 40 were in the CTP-C stage.

None of the CTP-A patients with cirrhosis had HRS. Of the total of 29 patients with HRS, 4 (13.8%) were in the CTP-B stage, and 25 (86.2%) were in the CTP-C stage. The majority of the patients with HRS were in the CTP-C stage (Table 1).

The grade of ascites, CTP scores, and MELD scores were significantly higher in contrast to hemoglobin levels; hematocrit concentrations were significantly lower in patients with type 1 and 2 HRS compared with patients with non-HRS stable cirrhosis. There were no statistical differences between the groups in terms of age, gender, bilirubin, albumin, international normalized ratio (INR), serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT). The demographic features and laboratory data of the study groups are shown in Table 2.

In the patients with HRS, there was a negative correlation between hemoglobin–hematocrit levels and serum creatinine (r=–0.542, p=0.002; r=–0.466, p=0.01, respectively). There was a positive correlation between serum creatinine and MELD and CTP scores, which are indicators of the degree of liver failure (r=0.472, p=0.01; r=0.369, p=0.04, respectively). Higher CTP and MELD scores, higher ascites grades, and lower hemoglobin and hematocrit levels were associated with higher creatinine levels and lower creatinine clearance. Particularly, these correlations were more prominent in the CTP-C group, which included the majority of the patients with HRS. As hemoglobin levels decreased and CTP scores increased, serum creatinine levels also increased and renal functions worsened in the patients with HRS (Figure 1).

Logistic regression analysis was performed by including hemoglobin levels, CTP scores, MELD scores, and grade of ascites for introduction to HRS. In this analysis, hemoglobin, CTP and MELD scores were statistically significant (Table 3).

During the six-month follow-up period, 31 patients (46.9%) died; ten died during hospitalization, while 21 died after being discharged from hospital.

Eight of the nine patients with type 1 HRS (88.8%), 12 of the 20 patients with type 2 HRS (60%), and 11 of the 37 patients with stable cirrhosis (29.7%) died during the six-month follow-up period. The mortality was higher in patients with HRS compared with those with stable non-HRS cirrhosis (p<0.001). Decreased hemoglobin, albumin, and eGFR levels and increased INR, SGOT, bilirubin, creatinine, and CTP/MELD scores showed a significant association with mortality in all patients with cirrhosis (p≤0.05 for all). Furthermore, for patients with HRS, hemoglobin, albumin, eGFR levels were lower, while creatinine, MELD scores, and CTP scores were higher in non-survivors compared with survivors (Table 4).

Table 1. HRS distribution in the CTP groups

	CTP-A	CTP-B	CTP-C
Type 1 HRS (n)	-	2	7
Type 2 HRS (n)	-	2	18
Total (n/%)	-	4 (13.8%)	25 (86.2%)

HRS: Hepatorenal Syndrome; CTP: Child–Turcotte–Pugh

Table 2. The demographic, clinical, and laboratory features of patients

	Type 1 HRS	Type 2 HRS	Non-HRS	p*
Age (median years)	65.89±8.87	66±8.38	61.43±11.28	0.208
Gender (M/F)	4/5	10/10	24/13	0.385
Hemoglobin (g/dL)	8.81±1.06	9.77±1.72	11.63±1.88[a,b]	<0.001
Hematocrit (%)	26.13±3.52	29.23±6.1	35.46±6.23[a,b]	<0.001
Platelet (×10³/μL)	72.22±27.18	110.25±49.28	139.84±64.06[a]	0.005
Creatinine (mg/dL)	2.96±0.57	1.89±0.3[a]	0.84±0.25[a,b]	<0.001
Estimated GFR	25.08±16.89	35.96±10.09	93.27±40.41[a,b]	<0.001
Albumin (g/dL)	2.62±0.41	2.59±0.4	2.96±0.47[b]	0.006
SGOT (ıu/L)	88.11±64.99	134.95±152.73	72.46±54	0.071
SGPT (ıu/L)	41.67±25.77	70.5±87.8	35.97±36.59	0.091
Total Bilirubin (mg/dL)	7.2±7.19	10.77±15.52	4.11±6.5	0.068
INR	1.96±0.48	2.19±1.03	4.11±0.78	0.130
CTP score	11.67±2	11.55±1.7	8.86±2.36[a,b]	<0.001
MELD score	29.78±6.96	26.35±7.75	15.46±6.19[a,b]	<0.001
Ascites (n)				
- Mild	0	2	6	<0.001
- Moderate	0	6	12	
- Tense	9	12	8	

*One-way ANOVA. Inter-group comparison with Bonferroni test:
[a]Compared with Type 1 HRS, p≤0.05;
[b]Compared with Type 2 HRS, p≤0.05.
HRS: Hepatorenal Syndrome; M: male; F: female; GFR: glomerular filtration rate; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; INR: international normalized ratio; CTP: Child–Turcotte–Pugh; MELD: model of end stage liver disease

DISCUSSION

To our knowledge, this is the first study that discusses the pathogenetic effects of anemia on HRS and renal dysfunction in patients with cirrhosis.

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Table 3. Logistic regression analysis for introduction to HRS

								95% CI for EXP (B)	
		B	S.E.	Wald	df	p	Exp (B)	Lower	Upper
Step 1a	Hemoglobin	–.706	.306	5.327	1	0.021 *	.494	.271	.899
	CTP	–.899	.453	3.932	1	0.047 *	.407	.167	.990
	MELD	.365	.119	9.362	1	0.002 *	1.441	1.140	1.821
	Ascites			2.874	3	.411			
	- Mild	–22.616	10593.053	.000	1	.998	.000	.000	.
	- Moderate	–.645	1.390	.216	1	.642	.525	.034	7.993
	- Tense	–1.737	1.025	2.871	1	.090	.176	.024	1.313
	Constant	9.924	5.437	3.331	1	.068	20407.809		

a: Variable(s) entered on step 1: hemoglobin, CTP, MELD_scores, ascites., * p≤0.05.
CTP: Child–Turcotte–Pugh; MELD: model of end stage liver disease

Table 4. Mean age and laboratory findings of survivors and non-survivors with HRS

Parameters	Survivors (n=9)	Non-survivors (n=20)	p
Age (years)	70.1±5.20	64.1±8.9	0.73
Hemoglobin (g/dL)	10.3±1.8	9.0±1.3	0.04 *
INR	1.7±0.4	2.3±0.9	0.10
Total Bilirubin (mg/dL)	4.0±5.1	12.1±15.3	0.04 *
Albumin (g/dL)	2.8±0.2	2.4±0.3	0.02 *
Creatinine (mg/dL)	1.8±0.3	2.4±0.6	0.01 *
eGFR (ml/min/1.73m^2)	39.7±13.2	29.3±12.2	0.05 *
MELD score	21.2±5.4	30.2±6.7	0.002 *
CTP score	10.1±1.6	12.2±1.4	0.001 *

*p≤0.05
INR: international normalized ratio; eGFR: estimated glomerular filtration rate; MELD: model of end stage liver disease; CTP: Child–Turcotte–Pugh

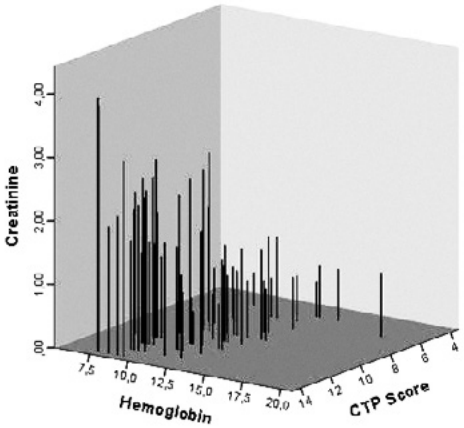

Figure 1. The relationship between creatinine levels, hemoglobin levels, and CTP scores in patients with HRS

The results revealed that patients with hepatorenal syndrome had significantly lower hemoglobin and hematocrit levels compared with non-HRS stable cirrhosis patients. Hemoglobin and hematocrit levels were also lower in patients with type 1 HRS compared to those with type 2 HRS. Patients with lower hemoglobin and hematocrit levels survived for shorter periods compared with patients with higher hemoglobin and hematocrit levels. These results support that anemia may play a potential or additive role in the pathogenesis of HRS. In other words, anemia may facilitate HRS and deteriorate renal functions in patients with HRS.

At present, the pathophysiologic mechanisms of HRS are not fully defined. The regulation of renal function is associated with several hemodynamic and physiologic factors. One of these is the liver. The liver plays an important role in the regulation of renal functions under normal conditions (12). In the non-cirrhotic condition, an uptake of amino acids by the liver stimulates and increases renal blood flow and glomerular filtration rate (13); this regulation is disrupted in patients with cirrhosis. However, the most important mechanisms are abnormal hemodynamics associated with portal hypertension and ascites in HRS. The chain of events triggered by portal hypertension includes splanchnic vasodilatation, underfilling of the arterial circulation, decreased effective blood volume, sympathetic system activation, hyperkinetic circulation, activated renin–angiotensin–aldosterone system, severe constriction of the renal vasculature, decreased renal perfusion, and glomerular filtration rate (GFR) (2-4). During this process, an imbalance between vasodilators (NO, glucagon, substance P) and vasoconstrictors (vasopressin, endothelins, leukotriene E2, F2-isoprostanes) contributes to the changes in the circulatory system (14-16). Particularly, NO has been proposed as a cause of both hyperdynamic circulatory changes and renal failure (4,5,17,18). These hemodynamic changes lead to renal ischemia and renal dysfunction in cirrhosis.

On the other hand, ischemia is the most common cause of renal failure. Ischemic-induced renal tissue hypoxia is thought to be a major component in the development of the initial tubular damage and acute renal failure (19). Anemia is an important

cause of tissue hypoxia or dysoxia. When the hemoglobin concentration inside red blood cells decreases, it also negatively affects the capacity of the blood to carry oxygen (20). In the case of anemia, the oxygen supply to the tissues can be reduced. Therefore, anemia may contribute to microcirculatory renal hypoxia and injury due to reduced oxygen supply to the kidneys. In addition, it is well known that anemia can also aggravate sympathetic activity and hyperdynamic circulation, which play important roles in the pathogenesis of HRS (7,8).

The major portion of the excess fluid in patients with cirrhosis is in the third space due to portal hypertension and low oncotic pressure caused by hypoalbuminemia. The total blood volume in patients with cirrhosis is 10% more than in normal people. Hemodilution increases the frequency and degree of anemia; however, the main causes of anemia in patients with cirrhosis are gastrointestinal losses (varices, erosions, and portal hypertensive gastropathy), splenomegaly, bone marrow depression, malnutrition, iron and vitamin deficiencies, and chronic disease (21). In other words, the pathogenesis of anemia in cirrhosis is multifactorial and is coupled with true red cell mass decrease. As the severity of liver disease increases, hemoglobin–hematocrit levels may decrease. Anemia may be associated with the severity of the liver disease, but this does not change the fact that anemia leads to microcirculatory renal tissue hypoxia and aggravates hyperdynamic circulation.

There are other examples that show the negative clinical implications of anemia. For example, Go et al. (22) found that reduced (<13 g/dL) hemoglobin levels and chronic kidney disease independently predict substantially increased risks of death and hospitalization in heart failure, regardless of the level of systolic function. Furthermore, they also concluded that randomized trials are required to evaluate whether raising hemoglobin levels can improve outcomes in chronic heart failure. They mentioned that probable mechanisms include increased peripheral and myocardial tissue hypoxia, enhanced levels of proinflammatory cytokines, accelerated progression of LV hypertrophy, activation of the sympathetic nervous system and renin–angiotensin–aldosterone axis, and fluid overload (23). According to a study by da Silveria, in patients with stable ischemic heart disease, the presence of anemia, even mild, is associated with a worse prognosis (24). Similarly, Muzarelli et al. (25) proved that anemia is an independent predictor of death and major clinical adverse events among elderly patients with stable symptomatic coronary artery disease. Severe anemia can cause low oxygen levels in the heart and can lead to heart attack. On the other hand, Milionis et al. (26) reported that anemia is common in acute ischemic stroke and is associated with cardiovascular comorbidities. They found that a low hemoglobin status independently predicts short- and long-term mortality.

All these studies show that anemia is associated with a negative clinical outcome, increased complications, and a worse prognosis and mortality in several diseases. Similar mechanisms and results associated with anemia may also be accepted for HRS.

Anemia is not defined as a precipitant factor for HRS. Variceal bleeding and anemia are different entities. Variceal bleeding is an acute insult for hemodynamia. While variceal bleeding causes acute volume depletion and hypoperfusion, anemia causes tissue oxygenation defects and chronic microcirculatory ischemia. If anemic hypoxia is a precipitating factor in HRS, erythrocyte suspensions might be beneficial in improving renal functions in HRS with other medical treatment modalities such as vasopressin analogs, albumin, and volume enlargements.

In conclusion, the role of anemia in HRS pathogenesis may be explained by two mechanisms. Firstly, anemic hypoxia can lead to microcirculatory renal ischemia in the kidneys. Secondly, anemia can also activate sympathetic activity and hyperdynamic circulation in the pathogenesis of HRS. Further studies are required to determine whether severe anemia is a precipitant factor for HRS.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.G.; Design - G.G.; Supervision - M.A., H.P., A.D.; Data Collection and/or Processing - G.G., Y.S., A.G., M.B., S.C., H.A.; Analysis and/or Interpretation - G.G., M.A., M.K., A.G.; Literature Review - G.G.; Writer - G.G.; Critical Review - M.A.

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