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CLINICAL ASPECTS AND PROGNOSIS EVALUATION OF CIRRHOTIC PATIENTS HOSPITALIZED WITH ACUTE KIDNEY INJURY

Medicine

Dr. Prashant Kumar Assistant Professor, Department of Medicine, DMCH, Darbhanga

Dr. Manish Kumar* Senior Resident, Department of Medicine, DMCH, Darbhanga *Corresponding author

Dr. U C Jha Associate Professor, Department of Medicine, DMCH, Darbhanga

ABSTRACT

Renal failure was more common in patients with cirrhosis than in a control population of bleeding patients without cirrhosis matched by age and severity of the bleeding episode. The development of renal failure and hypovolemic shock was the only independent predictors of in-hospital mortality. **Methods:** Study Population The clinical records of 192 consecutive episodes of upper-gastrointestinal bleeding in 178 patients with cirrhosis admitted to the liver unit of Hospital. Two year period were reviewed. **Results:** Renal failure developed in 20 of the 175 episodes (11.4%). Renal failure was transient in 8 patients (40%) and nontransient in the remaining 12 patients (60%). Ischemic hepatitis was observed in 7 of the 20 (35%) episodes with renal failure compared with only 6 of the 155 (4%) episodes in which renal failure did not develop (P .001). **Conclusion:** renal failure is a common event in patients with cirrhosis and gastrointestinal bleeding, the occurrence of which is mainly related to the severity of bleeding and baseline liver function.

KEYWORDS

Introduction

To assess the incidence, clinical course, predictive factors, and prognosis of renal failure in patients with cirrhosis and gastrointestinal bleeding, 175 consecutive episodes of gastrointestinal bleeding in 161 patients were analyzed. Renal failure occurred in 20(11%) episodes and was transient in 8 episodes and nontransient in 12. Renal failure was more common in patients with cirrhosis than in a control population of bleeding patients without cirrhosis matched by age and severity of the bleeding episode. Among 39 clinical and laboratory variables obtained at admission or during hospitalization related with the bleeding episode or with liver and renal function, the presence of hypovolemic shock, number of packed red blood cells transfused, Child-Pugh class at admission, and baseline platelet count were independent predictors of renal failure. The development of renal failure and hypovolemic shock was the only independent predictors of in-hospital mortality. Mortality rate among the 20 episodes with renal failure was 55% (11 deaths) as compared with only 3% (5 deaths) in the 155 episodes without renal failure (P < .01). The development of nontransient renal failure entailed a much greater mortality as compared with transient renal failure (10of 12 [83%] vs. 1 of 8 [12%]; P < .01The current study was undertaken to assess the incidence, clinical course, predictive factors, and short-termprognosis of renal failure after gastrointestinal bleeding in a large series of consecutive patients with cirrhosis seen in a specialized gastrointestinal unit of a tertiary care centre. Moreover, to investigate whether cirrhosis per se is a predisposing factor for the development of renal failure after gastrointestinal bleeding, the incidence of renal failure in patients with cirrhosis was compared with that of a group of noncirrhotic patients matched by age and intensity of the bleeding episode.

Methods

Study Population The clinical records of 192 consecutive episodes of upper-gastrointestinal bleeding in 178 patients with cirrhosis admitted to the liver unit of Hospital. Two year period were reviewed. Patients with a hospital stay or survival of less than 48 hours after bleeding (8 and 9 patients, respectively) were excluded fromthe analysis. Therefore, the study was performed in a total of 175 episodes of upper-gastrointestinal bleeding in 161 patients. Of them, 104 patients were receiving diuretics before admisssion, and 21 patients were receiving -blockers (10 of these latter patients were treated with a combination of -blockers and nitrates. The diagnosis of cirrhosis was based on liver histology (44 patients) or on a combination of physical signs and biochemical and ultrasonographic findings (117 patients). Upper-Gastrointestinal Bleeding. Clinically significant upper-gastrointestinal bleeding was defined as hematemesis and/or melena associated with a fall in hematocrit below 35% or a reduction of 6 points or greater compared with baseline hematocrit. Management and Follow-up Upon admission, patients were initially evaluated by the medical staff in the Emergency Unit, where physical examination and laboratory data were obtained and resuscitation was performed. Patients were then transferred either to a specialized hepatogastroenterology Intensive Care Unit or to the liver or GI ward, according to their clinical condition. An emergency uppergastrointestinal endoscopy was performed in the majority of patients within the first 12 hours of admission, and therapy was instituted according to the endoscopic findings. In brief, patients with uppergastrointestinal bleeding caused by esophageal varices were initially treated with emergency sclerotherapy associated with somatostatin administration. Patients with peptic ulcer (see below) either with active bleeding, visible vessel, or clot were treated with injection of sclerosing agents, followed by ranitidine or omeprazol. Patients not responding to these therapies were treated with alternative methods. All patients with cirrhosis received norfloxacin orally or through a nasogastric tube for 7 days to prevent bacterial infections. Laboratory determinations including blood-cell counts, and standard biochemical and renal tests were performed serially during hospitalization. Statistical Analysis Univariate analyses were performed to identify factors predictive of the development of renal failure and in-hospital mortality. Statistical analysis was performed with the statistical program SPSS version 8.0 (SPSS Inc., Chicago, IL). A control group of 73 patients with upper-gastrointestinal bleeding without cirrhosis was identified frompatients admitted during the same period. Twenty-five of these 73 patients (34%) had associated medical conditions: heart failure in 16, and diabetes mellitus in 9. The matching was finished when no more patients with cirrhosis could be matched with a noncirrhotic bleeding patient. Results are presented as mean SEM. All reported P values are 2-tailed. P .05 was considered to indicate statistical significance.

RESULTS

Baseline Characteristics of Patients With Cirrhosis and Gastrointestinal Bleeding. Demographic, clinical, and laboratory data and characteristics of the bleeding episode are shown in Table 1. Renal Failure. Renal failure developed in 20 of the 175 episodes (11.4%). Renal failure was transient in 8 patients (40%) and nontransient in the remaining 12 patients (60). Ischemic hepatitis was observed in 7 of the 20 (35%) episodes with renal failure compared with only 6 of the 155 (4%) episodes in which renal failure did not develop (P .001). A severe bacterial infection was present in 9 (associated with septic shock in 5) of the 20 (45%) episodes with renal failure compared with 36 of the 155 (23%) episodes in which renal failure did not develop (P .03). Three of the 20 patients (15%) had both ischemic hepatitis and a severe bacterial infection. Finally, 7 patients with renal failure (35%) had neither ischemic hepatitis nor severe bacterial infection. No significant

differences in the mean peak of serum creatinine were found between patients in these subgroups. Among the 39 variables analyzed, 21 were found to have predictive value for the development of renal failure in the univariate analysis. Patients who developed renal failure had more advanced liver disease, higher frequency of related complications, and greater severity of bleeding as compared with patients not developing renal failure (Table 2). On a multivariate analysis, variables with independent predictive value forthe development of renal failure were the presence of hypovolemic shock, the number of PRBC units transfused, ChildPugh class at admission, and baseline platelet count. The deaths occurred a mean of 42 3 days (range, 30-72 days) after the index episode of bleeding. Main causes of death were: bacterial infection in 5 patients, hypovolemic shock in 4, renal failure and liver failure in 3 patients each, and cerebrovascular disease in 1 patient. The development of renal failure correlated strongly with mortality. Mortality rate among the 20 episodes with renal failure was 55% (11 deaths) as compared with only 3% (5 deaths) in the 155 episodes without renal failure (P .01). The development of nontransient renal failure entailed a much greater mortality as compared with transient renal failure (10 of 12 [83%] vs. 1 of 8 [12%]; P .01). Among the 40 variables analyzed (39 plus the development of renal failure), 20 were found to have predictive value for in-hospital mortality in the univariate analysis. Patients who died had more advanced liver disease, higher frequency of related complications, greater severity of bleeding, and greater incidence of renal failure during hospitalization as compared with patients who survived . Comparison Between Patients With Upper-Gastrointestinal Bleeding With and Without Cirrhosis. As expected, no significant differences were found among the 2 groups in any of the parameters analyzed, except for a higher frequency of nonsteroidal anti-inflammatory drug ingestion in patients without cirrhosis. Despite the fact that the intensity of the bleeding episode was very similar in both groups, patients with cirrhosis showed a significantly greater incidence of renal failure and in-hospital mortality. Moreover, when a multivariate analysis was performed in these 2 groups, the independent predictors of the development of renal failure were the presence of cirrhosis, hypovolemic shock, and the severity of the bleeding episode.

Discussion

Although the importance of renal failure in the assessment of prognosis of patients with cirrhosis has already been demonstrated in several recent reports,5,12-14 the occurrence, characteristics, and prognostic value of renal failure in patients with cirrhosis and gastrointestinal bleeding has not specifically been assessed. The main findings of the current study are that renal failure is a relatively frequent event in these patients, particularly in the setting of a severe bleeding episode and advanced liver disease (i.e., Child-Pugh class C), and that its development is strongly associated with a very poor short term prognosis. An incidence of renal failure of 8% has been reported in another study including a similar number of patients with cirrhosis and gastrointestinal bleeding. Nevertheless, it should be emphasized that both groups had mean platelet counts below normal values. The etiology of renal failure was not specifically investigated in the current study, but several mechanisms could be proposed. However, it cannot be ruled out completely that these cases represent hepatorenal syndrome triggered by acute hypovolemia. Because at present there are no reliable tests to be used in the differential diagnosis between ATN and hepatorenal syndrome. the exact type of renal failure in these patients cannot be known. A very interesting and novel finding of the current study was that patients with cirrhosis and gastrointestinal bleeding had a significantly greater risk of developing renal failure compared with patients without cirrhosis matched for age and severity of the bleeding episode. Alternatively, it could also be speculated that for a similar degree of hypovolemia, patients with cirrhosis might develop a more marked activation of vasoconstrictor systems compared with patients without cirrhosis. Whichever the mechanisms are, our findings indicate that the cirrhotic kidneys are very sensitive to reductions in renal perfusion. A surprising, yet collateral, finding of this study was the extremely low frequency of renal failure in patients with gastrointestinal bleeding without cirrhosis (1%). We are not aware of any study specifically investigating renal failure following gastrointestinal bleeding, but we anticipated a greater frequency of this complication. Several reasons may account for this low frequency. Finally, as discussed before, the kidneys of noncirrhotic patients may be more resistant to hypovolemia compared with those of cirrhotic patients. The most important clinical observation of this study was that the occurrence of renal failure was an independent predictor of in-hospital mortality in patients with cirrhosis and gastrointestinal bleeding. This finding is in keeping with that of a previous report showing that the development of renal failure after bleeding was an independent predictor of both short- and long-termmortality. The prognosis was particularly poor in patients with persistent (nontransient) renal failure, who had an 83% in-hospital mortality rate, a figure similar to that of patients developing renal failure during spontaneous bacterial peritonitis (78%) and patients with type 1 hepatorenal syndrome (87%). Altogether, these findings indicate that the development of renal failure in cirrhosis, regardless of the cause and the precipitating factor, is associated with a dismal prognosis. Efforts should be made to prevent the development of renal failure in patients with cirrhosis and to develop effective therapies for this complication

Conclusion

Renal failure is a common event in patients with cirrhosis and gastrointestinal bleeding, the occurrence of which is mainly related to the severity of bleeding and baseline liver function. Renal failure is a strong predictor of mortality in patients with cirrhosis and gastrointestinal bleeding. Patients with advanced cirrhosis commonly develop disturbances in renal function, such as sodiumretention, water retention, and renal failure.1-4 Among them, renal failure is the most relevant in clinical practice, because its appearance usually entails a very poor prognosis.1-4 Several factors predisposing to the development of renal failure in patients with cirrhosis have been identified, including spontaneous bacterial peritonitis, large-volume paracentesis without intravenous administration of albumin, and treatment with several drugs, such as nonsteroidal anti-inflammatory drugs or aminoglycosides.3-5 Despite the high frequency and clinical importance of gastrointestinal bleeding in cirrhosis, no studies have so far been reported aimed at specifically assessing the relationship between bleeding and renal failure in patients with cirrhosis

TABLE 1. Demographic, Clinical, and Baseline Laboratory Data of All Patients With Cirrhosis and Gastrointestinal Bleeding

Demographic data	
Age (yr)	59 ± 1 (18-85)
Sex (male/female)	113 (70%)/48 (30%)
Etiology of cirrhosis (alcohol vs. nonalcohol)	55/161 (34%)/106/161 (66%)
Previous ascites	110/175 (63%)
Previous SBP	11/175 (6%)
Previous GIB	92/175 (53%)
Treatment with NSAIDs	11/175 (6%)
Treatment with diuretics	104/175 (59%)
Treatment with β-blockers ± nitrates	21/175 (12%)
Previous renal failure	7/175 (4%)
Liver disease and complications	
Child-Pugh class (A/B/C)	40/175 (22%)/78/175 (45%) 57/175 (33%)
Ascites at admission	79/175 (45%)
Encephalopathy at admission	54/175 (31%)
Bacterial infections during hospitalization	45/175 (26%)
Hepatocellular carcinoma	23/175 (13%)
Baseline laboratory parameters	
Bilirubin (mg/dL)	3.2 ± 0.3 (2-22)
Albumin (g/L)	28 ± 0.4 (14-42)
Prothrombin time (%)	57 ± 1 (20-100)
AST (IU/L)	162 ± 40 (13-3834)
ALT (IU/L)	77 ± 12 (7-1607)
Alkaline phosphatase (IU/L)	251 ± 16 (86-1422)
GGT (IU)	98 ± 10 (5-939)
Platelet count ($\times 10^9$ μ/L)	100.6 ± 4.8 (8-476)
Leucocyte count ($\times 10^3$ μ/L)	8.8 ± 0.4 (1.4-42.3)
Serum creatinine (mg/dL)	1.0 ± 0.05 (0.9-6.2)
BUN (mg/dL)	28 ± 1 (4.3-130)
Serum sodium (mEq/L)	135 ± 0.5 (102-149)
Serum potassium (mEq/L)	4.3 ± 0.2 (2.6-6.9)
Characteristics of the bleeding episode	
Intensity (moderate/severe/massive)	87 (50%)/46 (26%)/42 (24%)
Systolic pressure (mm Hg)†	114 ± 1 (60-160)
Diastolic pressure (mm Hg)†	60 ± 1 (30-90)
Mean aterial pressure (mm Hg)†	78 ± 1 (40-113)
Pulse rate (beats/min)†	92 ± 1 (55-150)
Shock	20/174 (11%)
PRBC (units)	3.4 ± 0.3 (0-21)
Baseline hematocrit (%)	28 ± 0.4 (10-35)
Baseline hemoglobin (g/L)	9.1 ± 0.1 (2.4-12.9)
Cause of GIB (esophagogastric varices/ other)	144/175 (82%)/31/175 (18%)
Early rebleeding	16/175 (9%)

TABLE 2. Variables With Significant Predictive Value for Development of
Renal Failure in the Univariate Analysis

Variables	Renal Failure	No Renal Failure	P
Previous GIB	15/20 (75%)	77/135 (49%)	.03
Previous renal failure	4/20 (20%)	3/135 (2%)	.001
Bacterial infection during hospitalization	9/20 (45%)	30/135 (23%)	.036
Intensity of GIB (massive)	16/20 (80%)	26/135 (19%)	<.0001
Shock	12/20 (60%)	8/135 (5%)	<.0001
Cause of GIB (variceal bleed)	13/20 (65%)	131/135 (84%)	.05
Ascites at admission	17/20 (85%)	62/135 (40%)	<.0001
Encephalopathy at admission	16/20 (80%)	38/135 (24%)	<.0001
Child-Pugh class C	16/20 (80%)	41/135 (26%)	<.0001
Systolic pressure (mm Hg)*	100 ± 4	116 ± 1	<.0001
Diastolic pressure (mm Hg)*	47 ± 2	61 ± 1	<.0001
Mean arterial pressure (mm Hg)*	65 ± 2	80 ± 1	<.0001
PRBC (units)	6.1 ± 0.9	3.1 ± 0.3	<.0001
Baseline laboratory parameters			
Bilirubin (mg/dL)	5.3 ± 1	2.9 ± 0.3	.0003
Prothrombin time (%)	44 ± 4	59 ± 1	<.001
AST (IU/L)	378 ± 311	107 ± 31	.0001
ALT (IU/L)	202 ± 80	60 ± 6.9	.0001
Platelet count ($\times 10^9$ μ/L)	135,550 ± 16,165	102,799 ± 4,958	.03
Leukocyte count ($\times 10^9$ μ/L)	12,935 ± 1643	8,338 ± 451	.001
BUN (mg/dL)	40 ± 6	26 ± 1.3	.002
Serum creatinine (mg/dL)	1.4 ± 0.3	0.9 ± 0.003	<.0001

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