Original Article

Effect of terlipressin on renal function in cirrhotic patients with acute upper gastrointestinal bleeding

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Background: Renal dysfunction is a serious morbidity in cirrhotic patients with acute upper gastrointestinal bleeding (AUGIB). Terlipressin is the first-line treatment choice for acute variceal bleeding and hepatorenal syndrome (HRS). This study aimed to assess the effect of terlipressin on renal function in patients with liver cirrhosis and AUGIB.

Methods: We retrospectively reviewed 40 cirrhotic patients with AUGIB treated with terlipressin by an attending physician between January 2016 and June 2018. We analyzed the change of renal function parameters, including cystatin C (CysC) and creatinine (Cr), during the use of terlipressin and after terlipressin was stopped. We also identified the factors associated with renal function improvement in patients without active bleeding during the use of terlipressin.

Results: During the use of terlipressin, CysC value was significantly reduced (1.3±0.8 *vs.* 1.1±0.7, P=0.001); Cr value was reduced, but the reduction was not statistically significant (68.8±24 *vs.* 65.5±23, P=0.817); the rate of CysC reduction was significantly higher in patients treated with terlipressin than those treated with somatostatin/octreotide (73.1% *vs.* 0%, P=0.005); the rate of Cr reduction was not significantly different between patients treated with terlipressin and somatostatin/octreotide (61.5% *vs.* 20%, P=0.148); no factor associated with CysC reduction was identified; higher hemoglobin, red blood cell, and platelet and lower prothrombin time and international normalized ratio at baseline were significantly associated with Cr reduction. After terlipressin was stopped, neither CysC nor Cr value was significantly reduced (P=0.852 and P=0.296).

Conclusions: Terlipressin may be beneficial on preventing renal function impairment in cirrhotic patients with AUGIB.

Keywords: Terlipressin; cirrhosis; bleeding; acute kidney injury (AKI); cystatin C (CysC)

Submitted Nov 10, 2019. Accepted for publication Feb 07, 2020.
doi: 10.21037/atm.2020.02.135
View this article at: http://dx.doi.org/10.21037/atm.2020.02.135

Introduction

Renal function impairment, even acute kidney injury (AKI) (1) or hepatorenal syndrome (HRS), may develop in cirrhotic patients with acute upper gastrointestinal bleeding (AUGIB) (1-3). This is primarily associated with systemic vascular resistance reduction secondary to splanchnic arterial vasodilatation in cirrhotic portal hypertension (4) and renal perfusion reduction secondary to blood loss after gastrointestinal bleeding (5,6). On the other hand, renal dysfunction significantly decreases the survival of cirrhotic patients (7,8).

Currently, terlipressin is the first-line treatment option for the management of acute gastro-esophageal variceal bleeding and HRS (9,10). Terlipressin is a vasopressin analogue composed by a synthetic 12 amino acid peptide that acts through the V1 receptors leading to splanchnic vasoconstriction, arterial blood volume elevation, and portal pressure reduction. It also acts through the V2 receptors which can deactivate renal and systemic vasoconstriction systems, thereby ameliorating glomerular filtration rate (GFR) and improving renal perfusion and function (11). Evidence suggests that terlipressin can decrease creatinine (Cr) by increasing Cr clearance (12-22), GFR, and urine sodium concentration (23) in patients with HRS (24,25). However, until now, there is no evidence regarding effect of terlipressin on renal function in cirrhotic patients with AUGIB. Herein, we conducted a retrospective study to analyze the renal function changes during and after the treatment of AUGIB with terlipressin and to identify the factors associated with AKI development (26).

Methods

Study design

This was a retrospective study at the Department of Gastroenterology of the General Hospital of Northern Theater Command (formerly General Hospital of Shenyang Military Area) from January 2016 to June 2018. The primary objective of the study was to evaluate the renal function changes in patients treated with terlipressin. The secondary objectives were to identify the factors associated with reductions of Cr and cystatin C (CysC) values and those associated with development of AKI. The study protocol conformed to the Declaration of Helsinki and was approved by the Medical Ethical Committee of our hospital [No. k(2018)20]. All included patients were treated by an attending physician (Xingshun Qi). Inclusion criteria were: (I) patients admitted with liver cirrhosis and AUGIB; and (II) patients received terlipressin treatment. Exclusion criteria were: (I) lack of renal function results, such as Cr and CysC; and (II) renal parenchymal disease. Additionally, to further explore the role of terlipressin on renal function improvement, we established a control group of cirrhotic patients treated with somatostatin/octreotide for AUGIB during the same enrollment period.

Data collection

All data were retrospectively reviewed by electronic medical charts. The primary data were collected as follows: age, sex, liver disease etiology, ascites, hepatic encephalopathy, hepatocellular carcinoma, hemoglobin, red/white blood cell count, neutrophils, lymphocytes, platelets, total bilirubin, direct bilirubin, alanine transaminase, aspartate transaminase (AST), albumin, D-Dimer, fibrinogen, prothrombin time, activated partial thromboplastin time, international normalized ratio, Cr, CysC, serum sodium, and total dose and duration of terlipressin treatment. Severity of liver dysfunction was assessed by Child-Pugh and model of end stage liver disease (MELD) scores.

Diagnosis and definitions

Liver cirrhosis diagnosis was primarily based on the history of liver diseases, clinical presentations, laboratory tests, and imaging examinations (27,28). AUGIB was diagnosed as a development of haematemesis and/or melena within 5 days before our admission (29). Baseline Cr and CysC values were defined as the Cr and CysC values obtained before the use of terlipressin at our admission. AKI was diagnosed as an increase of Cr value ≥26.5 μmol/L within 48 hours after our admission (30,31).

Classifications

According to the patients' conditions during the use of terlipressin or after terlipressin was stopped, the patients were divided into two groups: (I) patients at a stable condition, which was defined as the absence of further melena or hematemesis; and (II) patients at an unstable condition, which was defined as the presence of melena and/or hematemesis recurrence. According to the change of Cr value, the patients were divided into two groups: (I) patients with a Cr reduction; and (II) patients with a stable or increased Cr value. Similarly, according to the change of

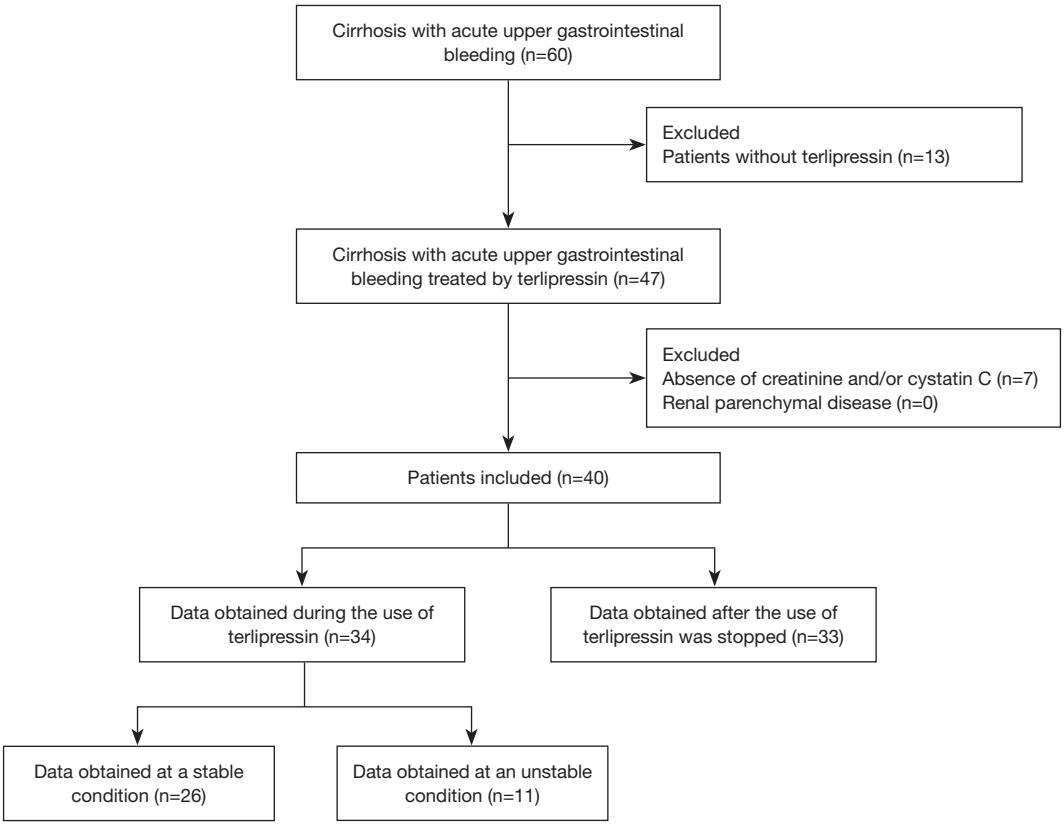

Figure 1 A flow chart of patient inclusion and exclusion.

CysC value, the patients were also divided into two groups: (I) patients with a CysC reduction; and (II) patients with a stable or increased CysC value.

Statistical analyses

Continuous data were expressed as the mean ± standard deviation and median (range). Categorical variables were expressed as frequencies (percentages). Continuous variables between two different patient groups were compared by the independent Student's *t*-test for normal distribution and non-parametric Mann-Whitney's test for non-normal distribution. Continuous variables before and after treatment were compared by the paired Student's *t*-test for normal distribution and non-parametric Wilcoxon test for non-normal distribution. Categorical variables were compared by the Chi-square test and Fisher exact test. P value less than 0.05 will be considered significant. Statistical analyses were performed using SPSS Statistics version 17.0.0. Before-after graphs were drawn to show the statistical differences by GraphPad Prism Software (La Jolla, CA, USA).

Results

Patient characteristics

A total of 40 patients (27 males and 13 females; mean age: 55.7±11 years) were included (*Figure 1*). Patient characteristics were shown in *Table 1*. The mean Cr and CysC values were 59.1±23.6 (range: 31.9–143.6) μmol/L and 1.2±0.8 (range: 0.6–4.1) mg/L, respectively. Upper gastrointestinal endoscopy was performed in 34 patients, of whom 88.2% had gastroesophageal varices related bleeding and 11.8% had peptic ulcer related bleeding.

Terlipressin

Thirty-eight and two patients were administered by continuous intravenous infusion alone and intravenous bolus followed by continuous intravenous infusion, respectively. The mean total dose of terlipressin was 12.3±7.6 (range:

Table 1 Characteristics of 40 patients treated with terlipressin

Variables	Mean ± SD or frequency (percentage)	Median (range)
Age (years)	55.7±11	57 [36–75]
Sex (male/female)	27 (67.5)/13 (32.5)	–
Ascites	26 (65.0)	–
Etiology of cirrhosis		–
Hepatitis B	11 (27.5)	–
Hepatitis C	3 (7.5)	–
Alcohol abuse	8 (20.0)	–
Autoimmune-related	2 (5.0)	–
Drug-related	3 (7.5)	–
Unknown	7 (17.5)	–
Hepatitis B + hepatitis C	1 (2.5)	–
Hepatitis B + alcohol abuse	2 (5.0)	–
Hepatitis C + alcohol abuse	2 (5.0)	–
Drug-related + autoimmune-related	1 (2.5)	–
Etiology of bleeding		–
Gastroesophageal varices related bleeding	30 (75.0)	–
Peptic ulcer related bleeding	4 (10.0)	–
No gastroscopy	6 (15.0)	–
Hepatic encephalopathy	2 (5.0)	–
Hepatocellular carcinoma	8 (20.0)	–
Child-Pugh score	7.8±2.2	7 [5–14]
MELD score	4.9±3.0	4.1 (0.9–15)
Red blood cell (10^{12}/L)	3.0±0.9	2.8 (1.6–5.6)
Hemoglobin (g/L)	81±25.6	74 [41–152]
White blood cell (10^9/L)	6.7±3.7	5.6 (1.5–17.1)
Neutrophil (10^9/L)	4.8±2.9	4.5 (0.8–13.8)
Lymphocyte (10^9/L)	1.3±1.0	1.0 (0.2–4.5)
Platelet (10^9/L)	110.8±91.2	80.5 [33–473]
Total bilirubin (μmol/L)	36.7±58.4	22 (8.1–361.5)
Direct bilirubin (μmol/L)	22.7±47.2	9.7 (3.5–292.9)
Alanine transaminase (U/L)	28.7±26.7	19.7 (8.1–145.7)
AST (U/L)	46.3±62.5	26.2 (3.5–390.9)
Albumin (g/L)	29.6±6.3	30.6 (5.7–39.1)
D-Dimer (mg/L)	2.3±3.2	1.1 (0.2–15.9)
Fibrinogen (g/L)	2.0±0.8	1.8 (0.6–4.4)

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Mean ± SD or frequency (percentage)	Median (range)
Prothrombin time (s)	18.4±4.1	16.9 (13.8–33.6)
Activated partial thromboplastin time (s)	41.7±7.9	41 (30–68.3)
International normalized ratio	1.5±0.4	1.4 (1.1–3.3)
Cr (μmol/L)	59.1±23.6	63.3 (31.9–143.6)
CysC (mg/L)	1.2±0.8	0.9 (0.6–4.1)
Serum sodium (mmol/L)	136.9±4.5	137.7 (121.8–144)
Cumulative defined daily dose (mg)	1.0±0.6	1 (0.2–3.3)
Total dose of terlipressin (mg)	12.3±7.6	11.5 [2–40]
Duration of terlipressin (days)	3.4±1.8	3 [1–9]

MELD, model of end stage liver disease; Cr, creatinine; CysC, cystatin C; AST, aspartate transaminase.

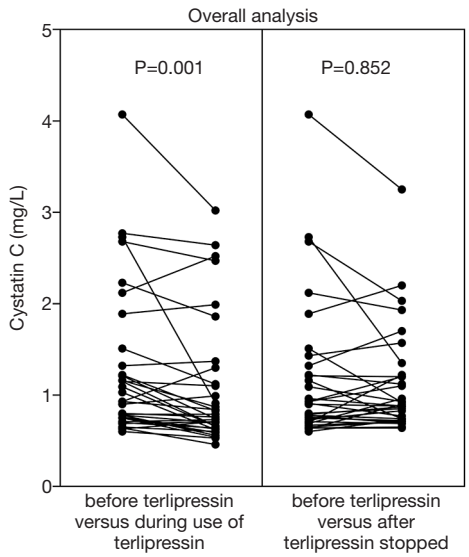

Figure 2 Change of cystatin C value during the use of terlipressin and after the use of terlipressin was stopped.

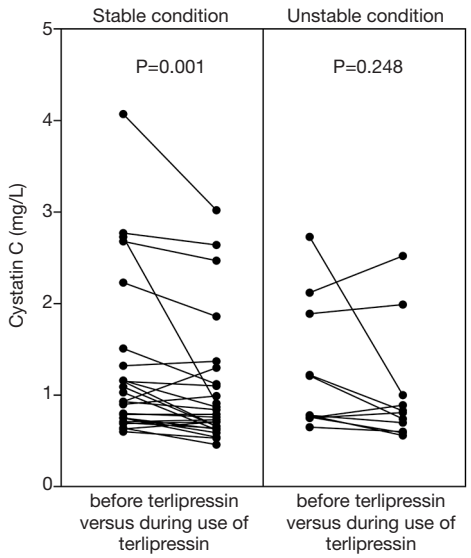

Figure 3 Change of cystatin C value in patients at a stable condition and at an unstable condition during the use of terlipressin.

2–40) mg. The mean duration of terlipressin was 3.4±1.8 (range: 1–9) days.

Change of CysC value during the use of terlipressin

CysC value was significantly reduced during the use of terlipressin in the overall analysis (1.3±0.8 *vs.* 1.1±0.7, P=0.001) (*Figure 2*, left panel). CysC reduction during the use of terlipressin remained significant in the subgroup analysis of patients at a stable condition (1.2±0.9 *vs.* 1.1±0.7, P=0.001) (*Figure 3*, left panel), but not in the subgroup analysis of patients at an unstable condition (1.2±0.7 *vs.* 1.0±0.6, P=0.248) (*Figure 3*, right panel). CysC value was reduced during the use of terlipressin in the subgroup analysis of patients with baseline CysC value ≥1.5 mg/L, but the reduction was not statistically significant (2.5±0.8 *vs.* 2.1±0.7, P=0.123) (*Figure 4*, left panel).

As only patients at a stable condition were included,

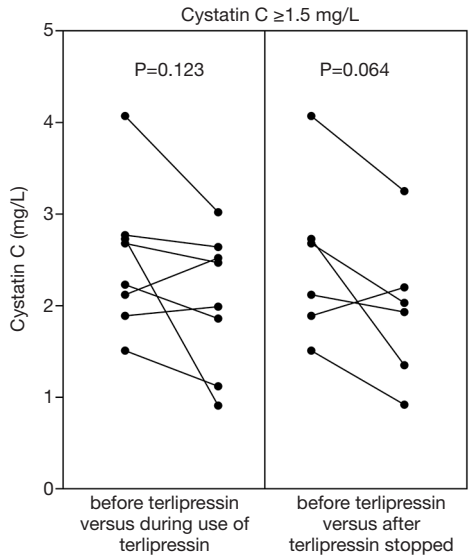

Figure 4 Change of cystatin C value in patients with baseline cystatin C value ≥1.5 mg/L during the use of terlipressin and after the use of terlipressin was stopped.

73.1% (19/26) of patients had a CysC reduction during the use of terlipressin; by comparison, no (0/5, 0%) patient had a CysC reduction during the use of somatostatin/octreotide without terlipressin. There was a statistically significant difference between the two groups (P=0.005). As only patients at a stable condition were included, no factor at baseline was significantly associated with CysC reduction during the use of terlipressin (*Table 2*).

Change of Cr value during the use of terlipressin

Cr value was mildly reduced during the use of terlipressin in the overall analysis (68.8±24 *vs.* 65.5±23, P=0.817) (*Figure 5*, left panel). Cr value was mildly reduced during the use of terlipressin in the subgroup analyses of patients at a stable condition (70.5±26.2 *vs.* 65.2±24.1, P=0.304) (*Figure 6*, left panel) and at an unstable condition (70.7±27.6 *vs.* 67.5±22.2, P=0.286) (*Figure 6*, right panel). Cr value was mildly reduced during the use of terlipressin in the subgroup analyses of patients with baseline Cr value ≥ 88.4 μmol/L (112.8±20.4 *vs.* 87.3±39.3, P=0.334) (*Figure 7*, left panel) and baseline Cr value ≥100 μmol/L (118.6±18.2 *vs.* 90.6±44.6, P=0.417) (*Figure 8*, left panel).

As only patients at a stable condition were included, 61.5% (16/26) of patients had a Cr reduction during the use of terlipressin; by comparison, 20% (1/5) of patients had a Cr reduction during the use of somatostatin/octreotide without terlipressin. There was no statistically significant difference between the two groups (P=0.148). As only patients at a stable condition were included, higher hemoglobin, red blood cell, and platelets and lower prothrombin time and international normalized ratio at baseline were significantly associated with Cr reduction during the use of terlipressin (*Table 3*).

Change of CysC value after the use of terlipressin was stopped

CysC value was mildly reduced after the use of terlipressin was stopped in the overall analysis (1.2±0.8 *vs.* 1.1±0.6, P=0.852) (*Figure 2*, right panel). CysC value was reduced after the use of terlipressin was stopped in the subgroup analysis of patients with baseline CysC value ≥1.5 mg/L, but the difference was not statistically significant (2.5±0.9 *vs.* 1.9±0.8, P=0.064) (*Figure 4*, right panel).

Seventeen (17/33, 51.5%) patients had a CysC reduction after the use of terlipressin was stopped; by comparison, 3 (3/9, 33.3%) patients had a CysC reduction after the use of somatostatin/octreotide was stopped. There was no statistically significant difference between the two groups (P=0.46). Higher MELD score and CysC value at baseline were significantly associated with CysC reduction after the use of terlipressin was stopped (*Table 4*).

Change of Cr value after the use of terlipressin was stopped

Cr value was not reduced after the use of terlipressin was stopped in the overall analysis (68.8±22.6 *vs.* 69.4±19.1, P=0.296) (*Figure 5*, right panel). Cr value was mildly reduced after the use of terlipressin was stopped in the subgroup analysis of patients with baseline Cr value ≥88.4 μmol/L (108.7±21.3 *vs.* 88.3±31.2, P=0.39) (*Figure 7*, right panel) and baseline Cr value ≥100 μmol/L (119±22.3 *vs.* 71.9±17.2, P=0.154) (*Figure 8*, right panel).

Thirteen (13/33, 39.4%) patients had a Cr reduction after the use of terlipressin was stopped; by comparison, 4 (4/9, 44.4%) patients had a Cr reduction after the use of somatostatin/octreotide was stopped. There was no statistically significant difference between the two groups (P=1.0). Higher Cr at baseline was significantly associated with Cr reduction after the use of terlipressin was stopped (*Table 5*).

Factors associated with the development of AKI

Three patients developed AKI during hospitalization. After excluding patients with AKI at admission or a baseline

Table 2 Factors associated with CysC reduction during use of terlipressin

Variables	CysC reduction (n=19)	No CysC reduction (n=7)	P value
Age (years)	53.6±10.5	59.7±11.9	0.214
Ascites	12 (63.2%)	4 (57.1%)	0.78
Hepatic encephalopathy	1 (5.3%)	1 (14.3%)	0.444
Hepatocellular carcinoma	6 (31.6%)	0	0.09
Sex (male/female)	13 (68.4%)/6 (31.6%)	5 (71.4%)/2 (28.6%)	0.883
Child-Pugh score	8.2±2.4	7.7±2.6	0.688
MELD score	5.6±3.6	4.5±2.5	0.707
Hemoglobin (g/L)	80.8±24.9	94.9±39.3	0.286
White blood cell (10^9/L)	6.1±2.9	6±3.1	0.933
Red blood cell (10^{12}/L)	2.8±0.8	3.2±1.1	0.325
Neutrophils (10^9/L)	4.3±2.2	4.5±2	0.823
Lymphocyte (10^9/L)	1.2±1	0.9±0.9	0.223
Platelet (10^9/L)	95.9±60	71.9±34.5	0.452
Total bilirubin (μmol/L)	49.9±81.8	24.5±9.6	0.977
Direct bilirubin (μmol/L)	32.9±66.5	15±9.5	0.885
Alanine transaminase (U/L)	33.6±33.3	32.5±26.9	0.885
AST (U/L)	61.9±84.8	45.4±35.2	0.977
Albumin (g/L)	30.2±3.8	30.8±5.5	0.811
Prothrombin time (s)	19±4.9	19±4.6	0.908
Activated partial thromboplastin time (s)	41.9±7.9	40.7±2.5	0.545
International normalized ratio	16±0.5	1.6±0.5	0.862
Cr (μmol/L)	75.1±28.5	58.2±13.2	0.148
CysC (mg/L)	1.4±1	0.9±0.2	0.118
Serum sodium (mmol/L)	136.7±4.2	134.2±6.1	0.246
Cumulative defined daily dose (mg)	1.2±0.8	0.8±0.5	0.271
Total dose of terlipressin (mg)	14.1±9.2	9.9±6	0.271
Duration of terlipressin (days)	3.8±2.1	2.7±2.1	0.185

MELD, model of end stage liver disease; Cr, creatinine; CysC, cystatin C; AST, aspartate transaminase.

Cr value ≥133 μmol/L (n=1), no factor at baseline was significantly associated with the development of AKI (*Table 6*).

Discussion

Major findings

First, our study found that the use of terlipressin could significantly reduce the CysC value and the benefit of terlipressin was significantly superior to that of somatostatin/octreotide. However, such a benefit seemed to disappear after terlipressin was stopped. Second, there was a Cr reduction during the use of terlipressin and the absolute benefit of terlipressin seemed to be larger than that of somatostatin/octreotide. However, such a benefit did not achieve a statistical significance. Third, it seemed that higher CysC and Cr values at baseline were associated with

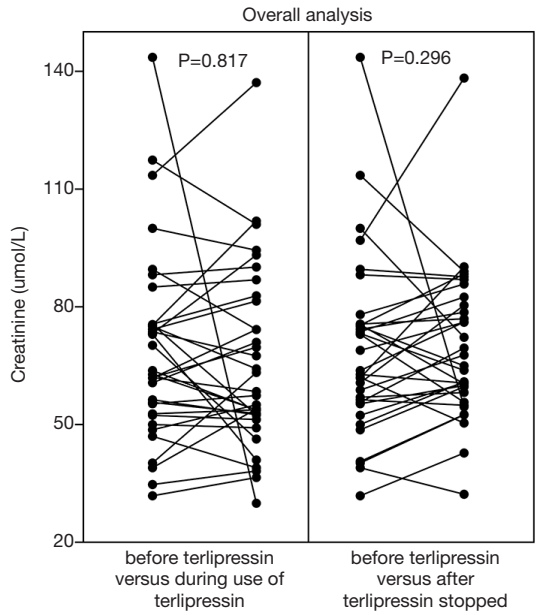

Figure 5 Change of creatinine value during the use of terlipressin and after the use of terlipressin was stopped.

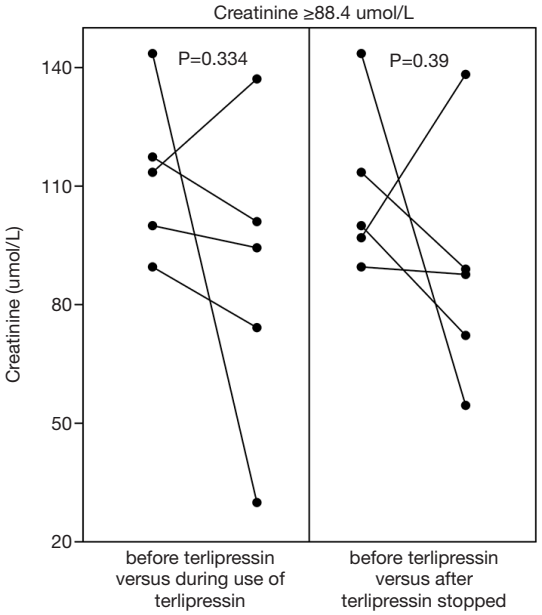

Figure 7 Change of creatinine value in patients with baseline creatinine value ≥88.4 μmol/L during the use of terlipressin and after the use of terlipressin was stopped.

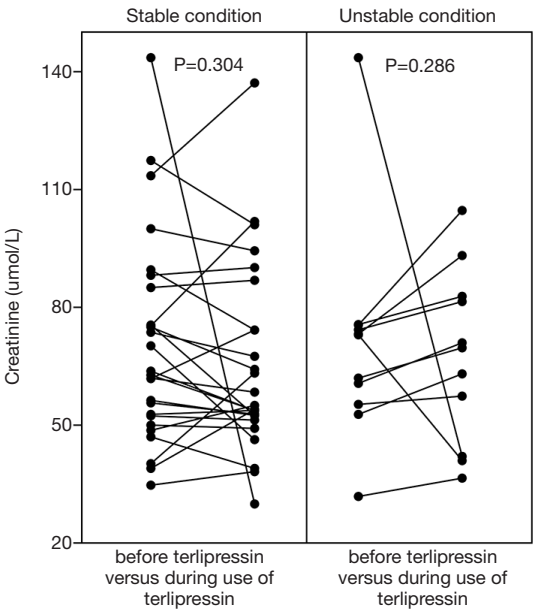

Figure 6 Change of creatinine value in patients at a stable condition and at an unstable condition during the use of terlipressin.

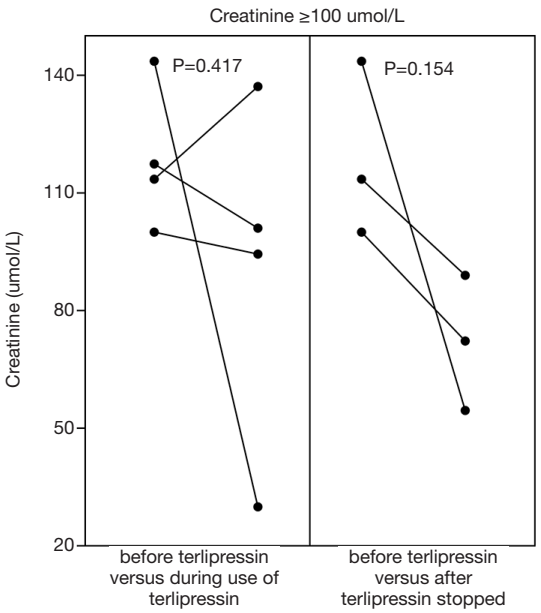

Figure 8 Change of creatinine value in patients with baseline creatinine value ≥100 μmol/L during the use of terlipressin and after the use of terlipressin was stopped.

Table 3 Factors associated with Cr reduction during use of terlipressin

Variables	Cr reduction (n=16)	No Cr reduction (n=10)	P value
Age (years)	55.9±11.6	54.2±10.4	0.714
Ascites	8 (50.0%)	8 (80.0%)	0.126
Hepatic encephalopathy	1 (6.3%)	1 (10.0%)	0.727
Hepatocellular carcinoma	4 (75.0%)	2 (20.0%)	0.768
Sex (male/female)	11 (68.75%)/5 (31.25%)	7 (70.0%)/3 (30.0%)	0.946
Child-Pugh score	7.8±2.6	8.5±2.2	0.378
MELD score	4.9±3.3	5.8±3.5	0.429
Hemoglobin (g/L)	93.9±30.4	69.7±21	0.038
White blood cell (10^9/L)	5.9±2.6	6.4±3.5	0.714
Red blood cell (10^{12}/L)	3.2±1	2.5±0.5	0.032
Neutrophil (10^9/L)	4.2±2.1	4.6±2.3	0.602
Lymphocyte (10^9/L)	1.2±0.7	1.1±1.3	0.153
Platelet (10^9/L)	105.9±58.5	63.1±37.1	0.016
Total bilirubin (μmol/L)	33.4±34.2	58.4±106.9	0.493
Direct bilirubin (μmol/L)	20.4±23.3	40.4±88.9	0.617
Alanine transaminase (U/L)	37.9±35.2	26±23.2	0.114
AST (U/L)	68.1±90.1	40.4±36.4	0.155
Albumin (g/L)	30.9±5.1	29.5±3.7	0.484
Prothrombin time (s)	17.7±4.9	21.1±3.7	0.015
Activated partial thromboplastin time (s)	41.3±7.2	42.1±6.5	0.785
International normalized ratio	1.5±0.5	1.8±0.4	0.019
Cr (μmol/L)	76.7±26.4	63.9±25.9	0.246
CysC (mg/L)	1.4±0.9	1.2±0.8	0.225
Serum sodium (mmol/L)	136.6±4.6	135±5.1	0.17
Cumulative defined daily dose (mg)	1.2±0.7	0.9±0.6	0.214
Total dose of terlipressin (mg)	14.4±9	10.5±7.5	0.354
Duration of terlipressin (days)	3.7±2.2	3.3±2	0.657

MELD, model of end stage liver disease; Cr, creatinine; CysC, cystatin C; AST, aspartate transaminase.

a higher probability of developing CysC and Cr reduction after the use of terlipressin was stopped. By comparison, CysC and Cr values at baseline might not be associated with CysC and Cr reduction during the use of terlipressin.

Prior studies

Few studies explored the effect of terlipressin on renal function parameters in cirrhotic patients with acute gastrointestinal bleeding. Based on our recent systematic review regarding terlipressin for treatment of acute variceal bleeding (32), only one previous randomized controlled trial reported the relevant data. The investigators included 163 patients treated with terlipressin and 161 patients treated with octreotide. Bleeding was controlled in 92.63% of patients treated with terlipressin and 95.6% of patients treated with octreotide. Notably, Cr was decreased from 1.2±0.8 mg/dL at baseline to 1.1±0.6 mg/dL after use of terlipressin (33).

Table 4 Factors associated with CysC reduction after use of terlipressin was stopped

Variables	CysC reduction (n=17)	No CysC reduction (n=16)	P value
Age (years)	56.5±10.1	56.7±10.4	0.965
Ascites	11 (64.7%)	10 (62.5%)	0.895
Hepatic encephalopathy	1 (5.9%)	1 (6.3%)	0.965
Hepatocellular carcinoma	3 (17.6%)	2 (12.5%)	0.68
Sex (male/female)	11 (64.7%)/6 (35.3%)	11 (68.75%)/5 (31.25%)	0.805
Child-Pugh score	8.4±2.3	7±2	0.077
MELD score	5.7±3.3	3.6±1.8	0.024
Hemoglobin (g/L)	75.9±19.1	83.3±29.6	0.399
White blood cell (10^9/L)	7.4±3.9	6.2±3.7	0.321
Red blood cell (10^{12}/L)	2.7±0.7	3.1±1.1	0.233
Neutrophil (10^9/L)	5.3±3.3	4.7±2.8	0.547
Lymphocyte (10^9/L)	1.5±0.9	1±0.9	0.182
Platelet (10^9/L)	125.5±101.3	101.8±94.6	0.139
Total bilirubin (μmol/L)	37.1±35.1	18.7±7	0.094
Direct bilirubin (μmol/L)	21.1±24.7	10.8±7.5	0.288
Alanine transaminase (U/L)	26.7±15.7	31.7±36.2	0.64
AST (U/L)	36.1±24.1	55±93.5	0.666
Albumin (g/L)	27.1±7	31.5±5.4	0.066
Prothrombin time (s)	19.1±5	17.3±2.5	0.46
Activated partial thromboplastin time (s)	42.1±9.4	41.2±6.2	0.815
International normalized ratio	1.6±0.6	1.4±0.3	0.449
Cr (μmol/L)	76±25.3	61.2±17.1	0.059
CysC (mg/L)	1.4±0.9	0.9±0.4	0.008
Serum sodium (mmol/L)	136.9±3.6	137.8±4.9	0.263
Cumulative defined daily dose (mg)	1.1±0.8	0.9±0.4	0.749
Total dose of terlipressin (mg)	13.5±9.4	10.9±4.8	0.759
Duration of terlipressin (days)	3.6±2.1	3.1±1.5	0.508

MELD, model of end stage liver disease; Cr, creatinine; CysC, cystatin C; AST, aspartate transaminase.

However, the data were not statistically compared. Additionally, one previous retrospective study from Taiwan reported that 30-day mortality was non-significantly higher in cirrhotic patients with esophageal variceal bleeding and renal function impairment receiving somatostatin than those receiving terlipressin (52.6% *vs.* 42.3%). However, the change of renal function parameters was not evaluated (7). By comparison, our study focused on the change of Cr and CysC values after terlipressin in such patients.

Why should we evaluate the outcomes of patients with normal Cr at baseline?

Recently, the diagnostic criteria of AKI have been changed. Traditional diagnostic criteria for AKI are that an increase of Cr is greater than 50% and the final value is greater than

Table 5 Factors associated with Cr reduction after use of terlipressin was stopped

Variables	Cr reduction (n=13)	No Cr reduction (n=20)	P value
Age (years)	58±7.5	55.7±11.6	0.494
Ascites	8 (61.5%)	13 (65.0%)	0.84
Hepatic encephalopathy	2 (15.4%)	0	0.07
Hepatocellular carcinoma	3 (23.1%)	2 (10.0%)	0.306
Sex (male/female)	9 (69.2%)/4 (30.8%)	13 (65.0%) /7 (35.0%)	0.801
Child-Pugh score	8.3±2.8	7.3±1.8	0.36
MELD score	5.8±3.6	3.9±2	0.062
Hemoglobin (g/L)	77.3±26.7	81±23.8	0.531
White blood cell (10^9/L)	7.9±4.1	6.1±3.5	0.101
Red blood cell (10^{12}/L)	2.6±0.9	3.1±0.9	0.151
Neutrophil (10^9/L)	6±3.4	4.4±2.7	0.117
Lymphocyte (10^9/L)	1.3±0.9	1.2±0.9	0.698
Platelet (10^9/L)	132.2±119.8	102.2±80.8	0.519
Total bilirubin (μmol/L)	34.9±38	23.8±16.1	0.754
Direct bilirubin (μmol/L)	21.8±25.1	12.4±13.1	0.376
Alanine transaminase (U/L)	30.7±23.7	28.1±30	0.606
AST (U/L)	42.2±32,2	47.2±82.9	0.357
Albumin (g/L)	28.9±5.1	29.5±7.5	0.58
Prothrombin time (s)	19.5±5.1	17.4±3	0.179
Activated partial thromboplastin time (s)	43.4±10.3	39.7±5.8	0.185
International normalized ratio	1.7±0.6	1.4±0.3	0.173
Cr (μmol/L)	80.9±26.9	61±15.4	0.011
CysC (mg/L)	1.5±1.1	0.9±0.3	0.197
Serum sodium (mmol/L)	136.3±5.3	138.1±3.4	0.253
Cumulative defined daily dose (mg)	1.1±0.8	0.9±0.5	0.897
Total dose of terlipressin (mg)	13.7±9.9	11.3±5.6	0.897
Duration of terlipressin (days)	3.8±2.3	3.1±1.4	0.224

MELD, model of end stage liver disease; Cr, creatinine; CysC, cystatin C; AST, aspartate transaminase.

1.5 mg/dL. Current diagnostic criteria for AKI have been updated as follows: (I) an increase of Cr within 48 hours is greater than or equal to 0.3 mg/dL; or (II) an increase of Cr within 48 hours is more than 1.5 times from the baseline; or (III) the urine volume lasts less than 0.5 mL/kg/h for 6 hours (30,31). In the contemporary era, AKI should be diagnosed by a dynamic increase of Cr, but not a fixed threshold of 1.5 mg/dL. AKI may occur even if an absolute level of Cr is within normal range. The status quo suggests that the diagnostic criteria for AKI are moving forward and interventions may be initiated in patients with normal Cr level.

A recent single-center study evaluated the impact of AKI in 385 patients with liver cirrhosis awaiting liver transplantation (34). Among them, 24% and 14% of patients with a baseline Cr level of ≤0.7 mg/dL developed AKI and death, respectively; and 37% and 19% of patients with a baseline Cr level of 0.7–0.97 mg/dL developed AKI and death,

Table 6 Factors associated with AKI

Variables	Occurrence of AKI during admission (n=3)	No occurrence of AKI during admission (n=36)	P value
Age (years)	61±4	57.5±11.4	0.147
Ascites	2 (66.7%)	23 (63.9%)	0.937
Hepatic encephalopathy	0	1 (2.8%)	0.77
Hepatocellular carcinoma	2 (66.7%)	7 (19.4%)	0.062
Sex (male/female)	3 (100%)/0	23 (63.9%)/13 (36.1%)	0.202
Child-Pugh score	7±1.7	7.5±1.9	0.687
MELD score	6±2.4	4.4±2.4	0.215
Hemoglobin (g/L)	89.7±19.7	82±26.2	0.51
White blood cell (10^9/L)	3.8±3.3	6.6±3.7	0.147
Red blood cell (10^{12}/L)	3.3±0.4	3±0.9	0.64
Neutrophil (10^9/L)	2.4±2.1	4.6±2.9	0.114
Lymphocyte (10^9/L)	0.9±1	1.3±1	0.369
Platelet (10^9/L)	75.3±55.2	113.6±95.1	0.343
Total bilirubin (μmol/L)	25.7±10.9	33±58.2	0.51
Direct bilirubin (μmol/L)	11.6±3.6	20.5±48	0.772
Alanine transaminase (U/L)	35.2±9.7	27.7±27.8	0.097
AST (U/L)	36.2±15.5	46.7±65.5	0.58
Albumin (g/L)	32.9±3.1	29.9±6.3	0.399
Fibrinogen (g/L)	1.5±0.9	2±0.8	0.356
Prothrombin time (s)	18.5±5.2	17.8±3.1	1
Activated partial thromboplastin time (s)	39.3±8.1	41.6±7.6	0.937
International normalized ratio	1.6±0.6	1.5±0.3	0.958
Cr (μmol/L)	82.6±12.4	65.9±20.7	0.18
CysC (mg/L)	1±0.4	1.2±0.8	0.937
Serum sodium (mmol/L)	136.8±2.7	137.4±4.5	0.329
Cumulative defined daily dose (mg)	1.5±1.6	0.9±0.5	0.617
Total dose of terlipressin (mg)	17.7±19.5	11±5.6	0.616
Duration of terlipressin (days)	3.3±3.2	3.1±1.5	0.746

AKI, acute kidney injury; MELD, model of end stage liver disease; Cr, creatinine; CysC, cystatin C; AST, aspartate transaminase.

respectively. It suggested the necessity of closely monitoring renal function and initiating the prophylactic measures of AKI in cirrhotic patients with normal Cr level (35). AUGIB is an important precipitating factor for AKI due to its secondary renal hypoperfusion. Thus, it might be necessary to prevent the development of AKI in cirrhotic patients with AUGIB when Cr level is normal. Our study found that terlipressin might improve renal function, especially CysC level, and potentially prevent AKI episodes in such patients.

Why has CysC, rather than Cr, been significantly improved?

Cr is a popular laboratory index for evaluating renal

Table 7 The risk factors of renal failure or AKI

Author, year	Study type	No. pts	Univariate analysis	Multivariate analysis	Pathogenesis	Outcomes
Makhlouf, 2012	Prospective study	159	Jaundice; encephalopathy; serum bilirubin (higher); serum albumin (lower); AST level (higher); bacterial infection; hepatocellular carcinoma; Child class C cirrhosis; shock; baseline urea (higher); Cr (higher)	Bacterial infection; total bilirubin (higher); serum albumin (lower); Child class C cirrhosis; shock; baseline urea (higher); Cr (higher)	Upper gastrointestinal bleeding	Renal failure
Fiaccadori, 2001	Prospective study	514	Platelet count (lower); liver cirrhosis; *de novo* acute renal failure; oliguria; non-cirrhotic chronic hepatic disease; Cr levels (higher); APACHE II score	NA	Acute gastrointestinal hemorrhage	Renal failure
Cárdenas, 2001	NA	161	Advanced liver disease; frequency of related complications (higher); bleeding (more serious)	Hypovolemic shock; packed red blood cells units transfused; baseline Child-Pugh class; baseline platelet count	Upper gastrointestinal bleeding	Renal failure
Cakmak, 2016	Retrospective study	245	Hypertension; chronic heart failure; malignancy; coronary artery disease; chronic kidney disease; albumin categorize; hemoglobin categorize	Chronic heart failure; malignancy; coronary artery disease; chronic kidney disease; albumin categorize	Upper-gastrointestinal bleeding	AKI

pts, patients; NA, not available; AKI, acute kidney injury; AST, aspartate transaminase.

function and an important component of MELD score for selecting the optimal liver transplantation candidate, but has many limitations (36). First, serum bilirubin had an impact on the Cr level. An increase of bilirubin level will lead to an underestimation of Cr level. Second, the muscle wasting and low protein intake resulted in a decreased synthesis of Cr. Third, ascites and peripheral edema may result in the attenuation of Cr in the body. By comparison, current evidence suggests the superiority of CysC over Cr in assessing renal dysfunction and its associated outcomes. First, five studies evaluated the role of CysC-based equation for estimating GFR in patients with cirrhosis and suggested that CysC-based equation achieved a better performance in estimation of GFR than Cr-based equation (26,37-40). Second, two studies evaluated the role of CysC for predicting the risk of HRS. One study found that CysC was the most significant predictor for HRS in cirrhotic patients with ascites and normal Cr level (41). Another study also found that baseline CysC was predictive of renal dysfunction and HRS in patients with acute decompensated cirrhosis (42). Third, four studies evaluated the role of CysC for diagnosing AKI in patients with cirrhosis. All of them found that CysC was a useful marker and predictor for diagnosing AKI (43-46). Lastly, three studies evaluated the role of CysC for predicting the mortality of cirrhotic patients with AKI. All of them suggested that CysC was superior to Cr or MELD score for predicting the mortality after AKI (45-47). Based on the literature review mentioned above and our findings that terlipressin could significantly improve the CysC value, we suggested the potential benefit of terlipressin for improving renal function in cirrhotic patients with AUGIB.

Risk factors for AKI

As shown in previous studies (6,48-50) (*Table 7*), risk factors of renal failure in AUGIB patients included worse hepatic and renal function, such as higher bilirubin, AST, and Cr, lower albumin, and Child-Pugh class C. The existence of comorbidity, such as shock, bacterial infection, oliguria,

hypertension, chronic heart failure, malignancy, coronary artery disease, and chronic kidney disease, was also a risk factor of renal failure in AUGIB patients. Unfortunately, our study did not identify any factor that was significantly associated with the development of AKI. This unexpected finding should be attributed to a small sample size (the number of included patients was only 40) and a few events of AKI (the number of patients with AKI was only 3).

Limitations

First, the main limitation of our study is a relatively small sample size which would affect the accuracy and stability of our findings. Second, we did not evaluate Cr clearance, urine sodium concentration, and GFR. Third, there is a risk of patient selection bias due to the retrospective nature of this study.

Conclusions

Terlipressin may be effective for improving renal function and preventing the occurrence of AKI in patients with cirrhosis and AUGIB. Certainly, we need further prospective studies with larger sample size to confirm the effect of terlipressin on renal function in patients with cirrhosis and AUGIB.

Acknowledgments

This work was partially presented as a poster presentation at the Asian Pacific Association for the Study of Liver (APASL) Single Topic Conference 2018 held in Beijing on December 6, 2018.
Funding: None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol conformed to the Declaration of Helsinki and was approved by the Medical Ethical Committee of our hospital [No. k(2018)20].

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Cite this article as: Zhang J, Liu J, Wu Y, Romeiro FG, Levi Sandri GB, Zhou X, Li M, Qi X. Effect of terlipressin on renal function in cirrhotic patients with acute upper gastrointestinal bleeding. Ann Transl Med 2020;8(6):340. doi: 10.21037/atm.2020.02.135

