Chapter

Serum Sodium Concentration in Patients with Portal Hypertension and Acute Gastrointestinal Bleeding Treated with Terlipressin: A Retrospective Observational Study

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Abstract

This retrospective observational study aimed to investigate the risk of serum sodium concentration in patients treated with terlipressin and attempted to explore the factors associated with serum sodium concentration. We included 17 patients with portal hypertension treated with terlipressin (Group 1), 7 with portal hypertension treated with somatostatin/octreotide (Group 2), 20 with acute non-variceal gastrointestinal bleeding treated with somatostatin/octreotide (Group 3), and 19 with acute pancreatitis treated with somatostatin/octreotide (Group 4). In all groups, serum sodium concentration at baseline was not significantly different from the lowest value during the infusion of terlipressin, somatostatin, or octreotide (Group 1: 136.95 ± 4.68 versus 135.52 ± 4.79, p = 0.426; Group 2: 139.64 ± 3.86 versus 138.41 ± 5.34, p = 0.813; Group 3: 138.02 ± 4.08 versus 137.69 ± 3.11, p = 0.630; Group 4: 135.96 ± 6.87 versus 134.60 ± 3.40, p = 0.098). The rate of serum sodium concentration reduction in Group 1 (8/17) was not significantly different from Group 2 (3/7, p = 1.000), Group 3 (11/20, p = 0.746), or Group 4 (14/19, p = 0.171). Age, sex, baseline MELD and Child-Pugh scores, cDDD value and duration of terlipressin, blood transfusion, and diuretics and paracentesis during terlipressin were not significantly associated with serum sodium concentration reduction in Group 1. In conclusion, serum sodium concentration is often reduced in patients treated with terlipressin. However, the association of sodium concentration reduction with terlipressin should be clarified.

Keywords: hyponatremia, terlipressin, sodium, portal hypertension, gastrointestinal bleeding

1. Introduction

Terlipressin is a prodrug of vasopressin, which transforms into vasopressin by enzymatic cleavage of the glycyl residues [1, 2]. It has been approved as the choice

of treatment for acute esophagogastric variceal bleeding (EGVB) [3–6]. Such a potent effect is mainly due to the activation of V1 receptors, which are dominantly located in the arterial smooth muscles of splanchnic circulation. The activation of V1 receptors causes the splanchnic vasoconstriction and thereby reduces the splanchnic blood flow and portal pressure [7]. In addition, terlipressin also activates the V2 receptors and increases the number of aquaporin-2 channels in the apical plasma membrane, thereby causing the water reabsorption in the renal collecting ducts [8]. This V2 receptor-mediated antidiuretic effect may result in dilutional hyponatremia. Mild to severe hyponatremia has been reported in a proportion of patients receiving terlipressin [9–12]. More notably, scattered case reports have also shown that patients with hyponatremia related to terlipressin develop the seizure [13–15].

Herein, this retrospective observational study aimed to investigate the risk of serum sodium concentration during terlipressin treatment and attempted to explore the factors associated with serum sodium concentration hyponatremia.

2. Materials and methods

Study protocol was reviewed and approved by the institutional review board of the General Hospital of Northern Theater Command (formally General Hospital of Shenyang Military Area).

2.1 Study population

All patients who were consecutively admitted to our department between February 2016 and November 2017 and were treated with terlipressin and/or somatostatin and/or octreotide by an attending physician (XQ) were considered as the study population.

Seventeen patients with portal hypertension who were diagnosed with acute gastrointestinal bleeding and were treated with terlipressin were considered as the experimental group (Group 1). Among them, 14 patients were diagnosed with liver cirrhosis due to hepatitis B virus alone (n = 5), hepatitis C virus plus alcohol abuse (n = 2), alcohol abuse alone (n = 2), autoimmune-related liver diseases alone (n = 2), drug-related liver diseases alone (n = 1), or unknown causes (n = 2); 4 patients had hepatocellular carcinoma; 15 patients underwent endoscopic examinations, of whom 6 and 9 had both esophageal and gastric varices and esophageal varices alone, respectively, but 2 patients refused; 9 patients received a combination of somatostatin (n = 6), octreotide (n = 1), and somatostatin plus octreotide (n = 2); 10 patients underwent endoscopic treatments, including esophageal variceal ligation alone (n = 6), esophageal sclerotherapy alone (n = 1), esophageal variceal ligation plus gastric tissue glue injection (n = 2), and esophageal sclerotherapy plus gastric tissue glue injection (n = 1).

Seven patients with portal hypertension who were diagnosed with acute gastrointestinal bleeding and were treated with somatostatin or octreotide but without terlipressin were considered as the first control group (Group 2). Among them, 6 patients were diagnosed with liver cirrhosis due to hepatitis B virus alone (n = 1), hepatitis B virus plus alcohol abuse (n = 2), alcohol abuse alone (n = 2), or unknown causes (n = 1); 2 patients had hepatocellular carcinoma; 6 patients underwent endoscopic examinations, of whom 3 and 3 had both esophageal and gastric varices and esophageal varices alone, respectively, but 1 patient was hemodynamically unstable and died before endoscopic examination; 4, 1, and 2 patients received somatostatin alone, octreotide alone, and somatostatin plus octreotide, respectively; and 5 patients underwent endoscopic treatments, including esophageal variceal

ligation alone (n = 2), gastric tissue glue injection alone (n = 1), and esophageal variceal ligation plus gastric tissue glue injection (n = 2).

Twenty patients treated with somatostatin or octreotide for acute non-variceal gastrointestinal bleeding were considered as the second control group (Group 3). Among them, 15 patients underwent endoscopic examinations. The causes of bleeding were peptic ulcer (n = 9), acute gastric mucosal lesions (n = 1), gastric cancer (n = 1), Mallory-Weiss syndrome (n = 1), post-resection of colonic polyps (n = 1), colon cancer (n = 2), gastric occupation (n = 1), or unknown causes (n = 5).

Nineteen patients treated with somatostatin or octreotide for acute pancreatitis were considered as the third control group (Group 4).

2.2 Terlipressin

Terlipressin (Ferring Pharmaceuticals, Kiel, Germany) was given by continuous intravenous infusion 1 mg every 6 hours in 16 patients and intravenous bolus 1 mg followed by continuous intravenous infusion 1 mg every 6 hours in 1 patient. Terlipressin can be maintained for a maximum of 5 days [16]. Terlipressin was discontinued till bleeding ceased for 72 hours (no hematemesis and melena) or patients received successful endoscopic treatments.

2.3 Somatostatin/octreotide

Somatostatin was given by continuous intravenous infusion 3 mg every 12 hours. Octreotide was given by continuous intravenous infusion 0.3 mg every 12 hours or subcutaneous injection 0.1 mg every 8 hours depending upon the severity of diseases. Somatostatin and octreotide can be used for 5 days or even longer [3]. As for patients with acute gastrointestinal bleeding, somatostatin or octreotide was discontinued till bleeding ceased for 72 hours (no hematemesis and melena) or patients received successful endoscopic treatments. As for patients with acute pancreatitis, somatostatin/octreotide was discontinued till abdominal symptoms disappeared, serum amylase and lipase levels returned to the normal range or was close to the normal range, inflammation parameters levels returned to the normal range, and peri-pancreatic exudation disappeared or remarkably reduced.

2.4 Data collection

Baseline data refer to the data recorded before terlipressin, somatostatin, or octreotide was initiated. They included demographic information; etiology of liver cirrhosis; major clinical presentations, such as hepatic encephalopathy, acute upper gastrointestinal bleeding, and ascites; major laboratory tests, such as white blood cell, hemoglobin, platelet count, total bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, serum creatinine, potassium, serum sodium, prothrombin time, activated partial thromboplastin time, international normalized ratio, D-Dimer, Model for End-Stage Liver Disease (MELD) and Child-Pugh scores, blood transfusion, amount of red blood cell transfused, diuretics and paracentesis, and duration of terlipressin, somatostatin, and octreotide.

We screened the hepatic and renal function, blood cell counts, and serum electrolytes during hospitalization depending upon the patients' profiles. The lowest serum sodium concentration was collected when terlipressin, somatostatin, or octreotide was being given.

We also recorded the first re-examination value during the infusion of terlipressin and the value after stopping the infusion of terlipressin.

2.5 Outcomes

The primary end point of the study was to investigate the changes of serum sodium concentration during the administration of terlipressin and/or somatostatin and/or octreotide. The changes of serum sodium concentration were compared (i.e., the baseline value versus the lowest value or the value after stopping the pharmacological treatment). The rate of serum sodium concentration reduction among groups was assessed.

In the Group 1, we evaluated the difference between the baseline and lowest value of serum sodium during the treatment and classified as sodium decreased and sodium stable or increased. The secondary end point was to assess the factors associated with serum sodium concentration reduction in patients treated with terlipressin for portal hypertension.

2.6 Statistical analysis

Continuous variables were presented as mean ± standard deviations and medians with ranges, and categorical variables as frequency (%). Comparison of continuous variables between groups was performed by using Mann-Whitney U-test and paired comparison rank sum test, and that of categorical variables by using Chi-square or Fisher's exact test. The statistical analyses were performed by using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 6.0 (7825 Fay Avenue, Suite 230, La Jolla, CA 92037, USA). $p < 0.05$ for the difference was statistically significant.

3. Results

3.1 Patient characteristics

Overall, 17, 7, 20, and 19 patients were included in Group 1, 2, 3, and 4, respectively (**Figure 1**). Characteristics of patients are shown in **Table 1**.

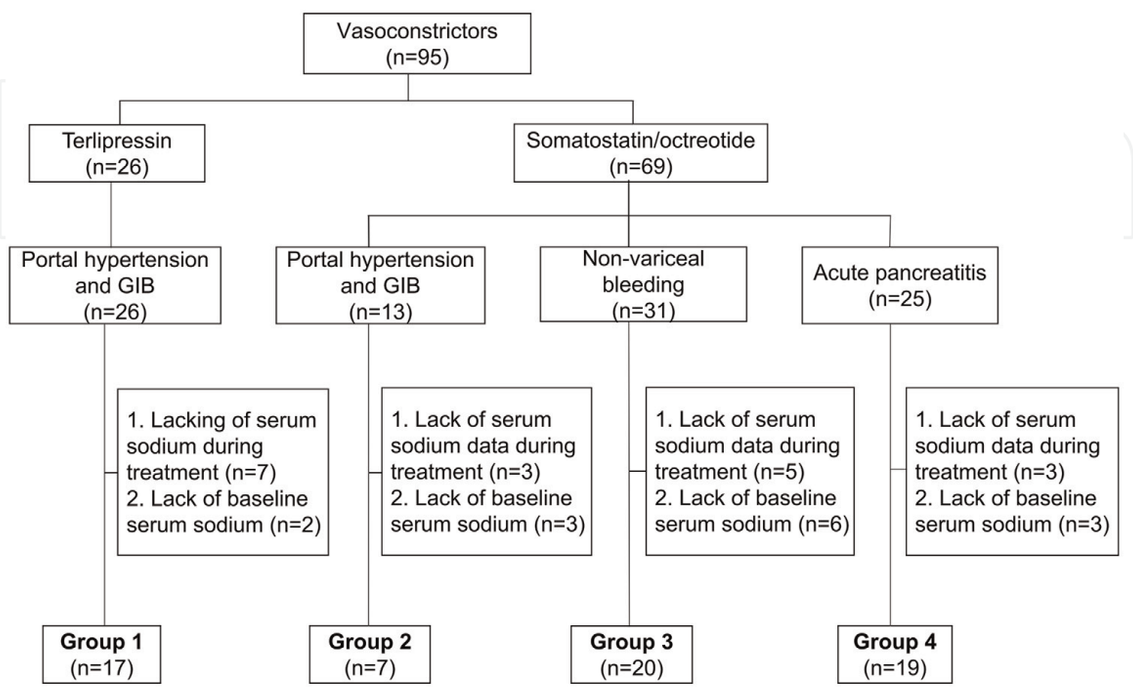

Figure 1.
Flow chart of patient enrollment. Abbreviations: GIB, gastrointestinal bleeding.

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Variables	Group 1			Group 2			Group 3			Group 4		
	No. pts	Mean ± SD or n (%)	Median (range)	No. pts	Mean ± SD or n (%)	Median (range)	No. pts	Mean ± SD or n (%)	Median (range)	No. pts	Mean ± SD or n (%)	Median (range)
Age (years)	17	58.06 ± 11.04	57 (34–75)	7	54.57 ± 9.54	52 (42–71)	20	59.10 ± 20.24	57 (20–93)	19	53.89 ± 20.53	49 (28–84)
Sex—male, n (%)	17	9 (52.9%)	—	7	6 (85.7%)	—	20	15 (75%)	—	19	14 (73.7%)	—
Clinical presentations												
Hepatic encephalopathy, n (%)	17	1 (5.9%)	—	7	0 (0)	—	20	—	—	19	—	—
Upper gastrointestinal bleeding, n (%)	17	17 (100%)	—	7	7 (100%)	—	20	17 (85%)	—	19	—	—
Ascites, n (%)	17	12 (70.6%)	—	7	1 (14.3%)	—	20	—	—	19	—	—
Laboratory tests												
White blood cell (10^9/L)	17	6.08 ± 3.92	4.9 (1.5–18.5)	7	5.4 ± 2.29	4.3 (2.2–8.4)	20	9.66 ± 5.54	8.65 (4.3–28.9)	19	9.42 ± 4.11	8.7 (2.1–16.5)
Hemoglobin (g/L)	17	71.65 ± 21.14	72 (37–124)	7	85.00 ± 17.25	79 (70–119)	20	93.95 ± 29.40	91.5 (48–136)	19	138.21 ± 31.10	135 (83–205)
Platelet count (10^9/L)	17	117.65 ± 93.00	82 (29–387)	7	115.14 ± 43.97	118 (59–174)	20	305.20 ± 274.58	238 (98–1287)	19	223.89 ± 87.69	221 (41–434)
Total bilirubin (umol/L)	17	28.25 ± 24.39	17.2 (8.1–92.3)	7	24.19 ± 14.83	16.6 (8.3–49.1)	20	12.29 ± 8.71	9.15 (3.5–33.7)	19	50.87 ± 59.56	19.6 (10–213.3)
Albumin (g/L)	17	29.09 ± 5.19	29.8 (18.7–39.1)	7	27.67 ± 5.21	25.6 (22–36.3)	20	34.24 ± 4.70	33.65 (24.8–41.5)	18	37 ± 6.46	37.4 (25.8–49.3)
Alanine aminotransferase (U/L)	17	22.41 ± 17.96	14.71 (10.13–77.1)	7	19.85 ± 7.34	22.02 (10.57–28.38)	20	17.93 ± 14.75	15.05 (4.57–65)	19	91.44 ± 97.24	49.12 (5.06–311.04)
Aspartate aminotransferase (U/L)	17	32.13 ± 18.14	25.05 (17.17–89.1)	7	33.00 ± 16.81	29.61 (17.88–65.85)	19	21.64 ± 12.29	15.5 (10.3–58)	19	83.15 ± 100.04	37.22 (13.79–369.2)
Blood urea nitrogen (mmol/L)	17	10.31 ± 5.54	9.39 (4.11–25.97)	7	7.44 ± 2.05	8.85 (3.86–9.05)	20	10.49 ± 6.14	8.79 (3.03–23.27)	19	5.72 ± 2.36	5.29 (2.09–11.21)
Serum creatinine (umol/L)	17	67.71 ± 21.71	62.78 (31.85–117.38)	7	107.67 ± 93.20	67.3 (52.65–314)	20	77.00 ± 27.05	67.05 (42–147)	19	66.02 ± 27.36	73.9 (18.32–129.9)
Potassium (mmol/L)	17	4.09 ± 0.69	3.84 (3.1–6.03)	7	4.07 ± 0.50	4.16 (3.33–4.64)	20	4.06 ± 0.48	3.99 (3.25–4.99)	19	4.01 ± 0.65	4.04 (2.86–5.84)
Sodium (mmol/L)	17	136.95 ± 4.68	137.4 (126.3–142.9)	7	139.64 ± 3.86	141.2 (132–142.7)	20	138.02 ± 4.08	138.35 (126.6–144)	19	135.96 ± 6.86	137.4 (115.1–142.6)
Prothrombin time (seconds)	17	17.13 ± 2.30	16.5 (15–23.9)	7	16.76 ± 2.23	17 (14.7–20.8)	19	14.90 ± 2.93	13.8 (12.9–24.9)	18	14.46 ± 3.26	13.3 (12–23.4)

Variables	Group 1			Group 2			Group 3			Group 4		
	No. pts	Mean ± SD or n (%)	Median (range)	No. pts	Mean ± SD or n (%)	Median (range)	No. pts	Mean ± SD or n (%)	Median (range)	No. pts	Mean ± SD or n (%)	Median (range)
Activated partial thromboplastin time (seconds)	17	38.21 ± 5.11	37.4 (29–47.8)	7	39.07 ± 4.25	40.2 (34.6–44.5)	19	33.56 ± 5.67	33.1 (25.6–47.9)	18	35.68 ± 6.20	34.6 (29.2–50.1)
International normalized ratio	17	1.45 ± 0.30	1.34 (1.16–2.08)	7	1.38 ± 0.25	1.39 (1.14–1.83)	19	1.17 ± 0.31	1.05 (0.95–2.24)	18	1.32 ± 0.34	1 (0.88–2.08)
D-Dimer (mg/L)	17	2.09 ± 2.23	1.09 (0.15–7.39)	7	1.85 ± 2.29	1.02 (0.38–6.86)	19	2.90 ± 10.40	0.33 (0.1–45.81)	17	2.42 ± 2.70	1.51 (0.24–9.38)
Model for end-stage liver disease score	17	8.23 ± 4.68	8.58 (0.9–16.84)	7	10.48 ± 5.60	11.05 (3.1–19.72)	—	—	—	—	—	—
Child-Pugh score	17	7.76 ± 1.92	7 (5–12)	7	7.14 ± 1.77	7 (5–10)	—	—	—	—	—	—
Duration of terlipressin (days)	17	3.15 ± 1.18	3 (1.25–5)	—	—	—	—	—	—	—	—	—
Duration of somatostatin or octreotide (days)	—	—	—	7	6.79 ± 4.58	6.5 (1.5–14.5)	20	3.88 ± 2.54	3 (0.25–12)	19	10.36 ± 5.14	10 (2–20)
Blood transfusion, n (%)	17	11 (64.7%)	—	7	4 (57.1%)	—	20	9 (45.0%)	—	—	—	—
Amount of red blood cell transfused (U)	11	5.06 ± 1.77	5 (2–8)	4	3.38 ± 1.38	3.25 (2–5)	9	2.39 ± 1.43	2 (1–5.5)	—	—	—

Group 1, terlipressin in portal hypertension;
Group 2, somatostatin or octreotide in portal hypertension;
Group 3, somatostatin or octreotide in non-variceal gastrointestinal bleeding;
Group 4, somatostatin or octreotide in acute pancreatitis.

Table 1.
Characteristics of patients.

3.2 Change in serum sodium concentration

Group 1. Serum sodium concentration before the infusion of terlipressin was not significantly different from the lowest value during the infusion of terlipressin (136.95 ± 4.68 versus 135.52 ± 4.79, $p = 0.426$) (**Figure 2A**), the first re-examination value during the infusion of terlipressin (136.24 ± 4.97, $p = 0.989$) (**Figure 2B**), or the value after stopping the infusion of terlipressin (136.29 ± 2.86, $p = 0.926$) (**Figure 2C**).

Group 2. Serum sodium concentration before the infusion of somatostatin or octreotide was not significantly different from the lowest value during the infusion of somatostatin or octreotide (139.64 ± 3.86 versus 138.41 ± 5.34, $p = 0.813$) (**Figure 2D**).

Group 3. Serum sodium concentration before the infusion of somatostatin or octreotide was not significantly different from the lowest value during the infusion of somatostatin or octreotide (138.02 ± 4.08 versus 137.69 ± 3.11, $p = 0.630$) (**Figure 2E**).

Group 4. Serum sodium concentration before the infusion of somatostatin or octreotide was not significantly different from the lowest value during the infusion of somatostatin or octreotide (135.96 ± 6.87 versus 134.60 ± 3.40, $p = 0.098$) (**Figure 2F**).

3.3 Percentage of patients who developed serum sodium concentration reduction among groups

The percentage of patients who developed serum sodium concentration reduction in Group 1 (8/17, 47.1%) was not significantly different from Group 2 (3/7,

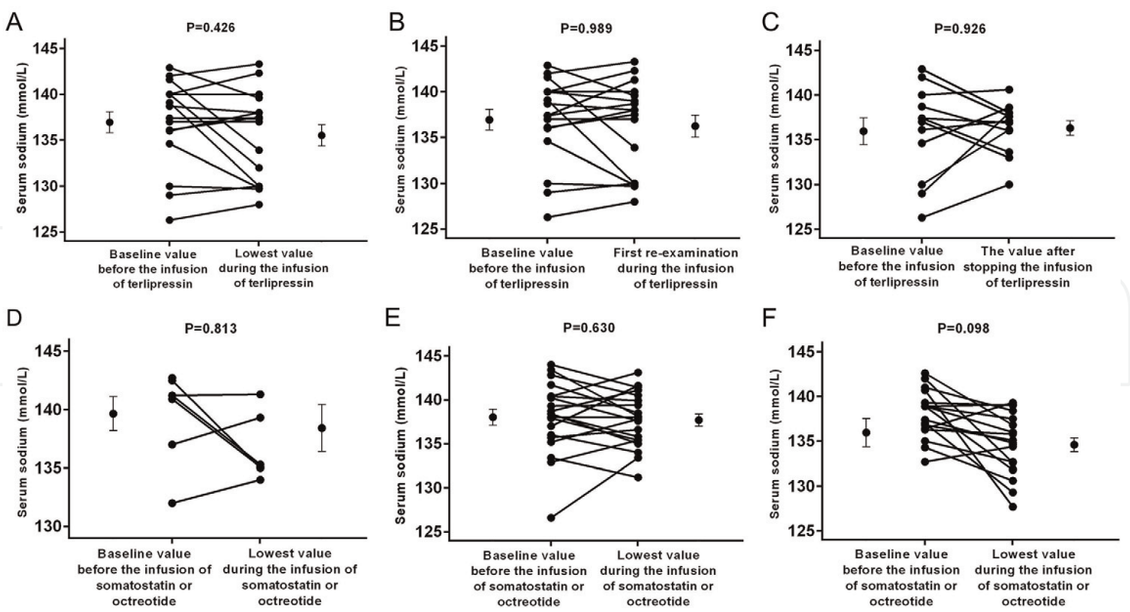

Figure 2.
Change in serum sodium concentration. (A) Serum sodium concentration before the infusion of terlipressin versus the lowest value during the infusion of terlipressin in Group 1. (B) Serum sodium concentration before the infusion of terlipressin versus the first re-examination value during the infusion of terlipressin in Group 1. (C) Serum sodium concentration before the infusion of terlipressin versus the value after stopping the infusion of terlipressin in Group 1. (D) Serum sodium concentration before the infusion of somatostatin or octreotide versus the lowest value during the infusion of somatostatin or octreotide in Group 2. (E) Serum sodium concentration before the infusion of somatostatin or octreotide versus the lowest value during the infusion of somatostatin or octreotide in Group 3. (F) Serum sodium concentration before the infusion of somatostatin or octreotide versus the lowest value during the infusion of somatostatin or octreotide in Group 4.

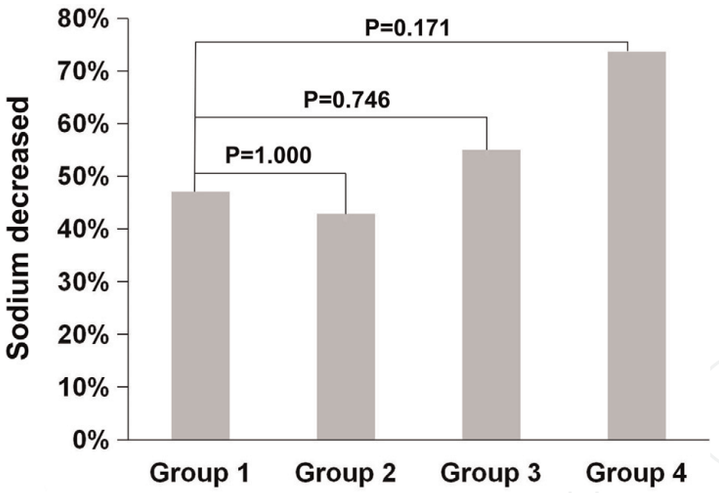

Figure 3.
Percentage of patients who developed serum sodium concentration reduction among groups.

42.9%, $p = 1.000$), Group 3 (11/20, 55%, $p = 0.746$), or Group 4 (14/19, 73.7%, $p = 0.171$) (**Figure 3**).

3.4 Factors associated with serum sodium concentration reduction in Group 1

Age, sex, baseline MELD and Child-Pugh scores, cDDD value and duration of terlipressin, blood transfusion, and diuretics and paracentesis during terlipressin were not significantly associated with serum sodium concentration reduction (**Table 2**).

Variables	Sodium decreased			Sodium stable or increased			P value
	No. pts	Mean ± SD or n (%)	Median (range)	No. pts	Mean ± SD or n (%)	Median (range)	
Age (years)	8	57.38 ± 10.18	59 (44–73)	9	58.67 ± 12.34	57 (34–75)	0.819
Sex—male, n (%)	8	3 (37.5%)	—	9	6 (66.7%)	—	0.347
Clinical presentations							
Hepatic encephalopathy, n (%)	8	0	—	9	1 (11.1%)	—	1.000
Upper gastrointestinal bleeding, n (%)	8	8 (100%)	—	9	9 (100%)	—	—
Ascites, n (%)	8	5 (62.5%)	—	9	7 (77.8%)	—	0.620
Laboratory tests							
White blood cell (10^9/L)	8	5.38 ± 2.23	4.7 (2.9–8.5)	9	6.72 ± 5.04	5 (1.5–18.5)	0.773
Hemoglobin (g/L)	8	74.5 ± 7.45	74 (64–85)	9	69.11 ± 28.80	60 (37–124)	0.360
Platelet count (10^9/L)	8	113.13 ± 63.75	92.5 (40–237)	9	121.67 ± 117.06	76 (29–387)	0.441
Total bilirubin (umol/L)	8	30.91 ± 25.64	25.5 (12.8–92.3)	9	25.87 ± 24.52	13.4 (8.1–79.9)	0.248

Variables	Sodium decreased			Sodium stable or increased			P value
	No. pts	Mean ± SD or n (%)	Median (range)	No. pts	Mean ± SD or n (%)	Median (range)	
Albumin (g/L)	8	29.06 ± 5.92	29.4 (18.7–39.1)	9	29.11 ± 4.81	29.8 (19–35.3)	0.847
Alanine aminotransferase (U/L)	8	23.35 ± 22.08	16.67 (10.13–77.1)	9	21.58 ± 14.73	14.69 (11.89–56.9)	0.923
Aspartate aminotransferase (U/L)	8	30.91 ± 12.85	25.51 (17.17–52.5)	9	33.21 ± 22.60	24.64 (17.22–89.1)	0.773
Blood urea nitrogen (mmol/L)	8	11.1 ± 6.54	9.6 (4.56–25.97)	9	9.60 ± 4.77	9.24 (4.11–18.83)	0.700
Serum creatinine (umol/L)	8	70.38 ± 30.66	68.53 (31.85–117.38)	9	65.33 ± 10.31	62.78 (50–78.35)	0.847
Potassium (mmol/L)	8	4.22 ± 0.76	4.01 (3.72–6.03)	9	3.98 ± 0.64	3.8 (3.1–5.21)	0.290
Sodium (mmol/L)	8	138.04 ± 4.12	138.9 (130–142.9)	9	135.98 ± 5.17	137 (126.3–142)	0.359
Prothrombin time (seconds)	8	16.95 ± 2.02	16.25 (15–20.4)	9	17.29 ± 2.63	16.8 (15.1–23.9)	0.629
Activated partial thromboplastin time (seconds)	8	39.06 ± 6.12	39.7 (30.6–47.8)	9	37.44 ± 4.26	37.3 (29–44.8)	0.501
D-Dimer (mg/L)	8	2.14 ± 2.13	1.3 (0.37–6.45)	9	2.05 ± 2.44	1.07 (0.15–7.39)	0.630
Ammonia (umol/L)	7	49.57 ± 19.44	53 (9–71)	8	50 ± 18.75	56.5 (19–72)	0.772
Model for End-Stage Liver Disease score	8	8.61 ± 5.69	9.49 (0.9–16.84)	9	7.87 ± 3.88	7.56 (1.94–15.06)	0.847
Child-Pugh score	8	7.75 ± 2.12	7 (6–12)	9	7.78 ± 1.86	8 (5–11)	0.807
cDDD value of terlipressin	8	1.15 ± 0.46	1.13 (0.5–1.67)	9	1.01 ± 0.41	1 (0.42–1.67)	0.530
Duration of terlipressin (days)	8	3.25 ± 1.22	3.13 (1.5–5)	9	3.03 ± 1.22	3 (1.25–5)	0.699
Blood transfusion, n (%)	8	4 (50%)	—	9	7 (77.8%)	—	0.335
Amount of red blood cell transfused (U)	4	4.5 ± 1.73	5 (2–6)	7	5.39 ± 1.84	5.2 (2–8)	0.331
Diuretics during terlipressin, n (%)	8	1 (12.5%)	—	9	1 (11.1%)	—	1.000
Paracentesis during terlipressin, n (%)	8	0	—	9	0	—	—

Table 2.
Factors associated with serum sodium concentration reduction in patients treated with terlipressin.

4. Discussion

In the present study, approximately half of our patients receiving terlipressin developed serum sodium concentration reduction after short-term treatment with terlipressin (3.15 ± 1.18 days). The incidence of hyponatremia or serum sodium concentration reduction was often heterogeneous among studies due to the characteristics of patients enrolled; definitions of hyponatremia or serum sodium concentration reduction; and indications, approaches, durations, and dosages of terlipressin. In randomized controlled trials regarding terlipressin for the treatment of EGVB, the incidence of hyponatremia, which was defined as serum sodium <130 mmol/L, was 0–6% [17–20]. Sola et al. [10] found that the incidence of serum sodium decreased >10 mmol/L from the baseline was 36% (21/58) in patients with EGVB treated by terlipressin for 5 days. Yim et al. [12] found that the incidence of serum sodium decreased >10 mmol/L from the baseline was 26.5% (40/151) in patients with EGVB treated by terlipressin for 5 days. Kang et al. [11] also reported that the incidence of serum sodium decreased >5 mmol/L from the baseline was 35.4% (45/127) during or after terlipressin treatment in patients with EGVB and hepatorenal syndrome (HRS).

Theoretically, terlipressin can induce the reduction of serum sodium concentration, because it activates the V2 receptors, thereby increasing the number of aquaporin-2 water channels in the apical plasma membrane and causing the water reabsorption in the renal collecting ducts [8]. However, there is little effect of terlipressin on V2 receptors, which is equal to only 3% of antidiuretic effect of vasopressin [13]. Indeed, the present study did not find any severe hyponatremia in our patients receiving terlipressin. Additionally, serum sodium concentration change (i.e., the baseline value versus the lowest value or the first re-examination value) was not statistically significant in all patients receiving terlipressin.

Somatostatin and its analogues cause the splanchnic vasoconstriction mainly by inhibiting the production and release of vasodilators, such as glucagon and vasoactive intestinal peptide, to reduce the portal pressure [6, 21]. They do not cause the change of serum sodium concentration. Thus, in order to further explore the effect of terlipressin on serum sodium concentration, the present study also compared the risk of serum sodium concentration reduction between patients receiving terlipressin and those receiving somatostatin or octreotide. We found that serum sodium concentration change in patients receiving terlipressin was not different from those receiving somatostatin or octreotide. These findings also suggested little effect of terlipressin on serum sodium concentration.

Several previous studies reported the risk factors for hyponatremia due to terlipressin. In 2010, Sola et al. [10] found that high baseline serum sodium level and low MELD score were independent risk factors for decreased serum sodium level. In 2013, Kang et al. [11] found that high baseline serum sodium level was an independent risk factor for hyponatremia. In 2015, Yim et al. [12] found that younger age, lower Child-Pugh score, higher baseline serum sodium, and long-term use of terlipressin (>5 days) were independent risk factors for hyponatremia and that lower body mass index and Child-Pugh score and higher baseline serum sodium were independent risk factors for rapid and severe hyponatremia. In 2017, Kim et al. [9] found that hepatitis B, diabetes mellitus, baseline serum sodium and creatinine levels, and shock at admission were independent risk factors for hyponatremia. Taken together, higher baseline serum sodium level and better liver function (low MELD or Child-Pugh score) are risk factors for hyponatremia during the treatment with terlipressin. In patients with more severe liver dysfunction, the portal pressure might be higher and the release of endogenous vasopressin was increased, thereby occupying the V2 vasopressin receptor. Thus, the antidiuretic

effect of terlipressin is compromised. We attempted to explore the baseline factors associated with serum sodium concentration reduction during terlipressin. Unfortunately, the duration of terlipressin, cDDD value of terlipressin, blood transfusion, amount of blood transfusion, and diuretics and paracentesis during terlipressin were not significantly associated with serum sodium concentration reduction. Certainly, this analysis should be performed again in a larger number of patients.

The duration, dosage, and route of terlipressin may be also associated with the risk of hyponatremia related to terlipressin. Bruha et al. [22] conducted a multicenter randomized double-blind study to compare the efficacy and safety of 10-day versus 5-day terlipressin for the treatment of EGVB, and found that prolonged terlipressin treatment was the only risk factor of hyponatremia. Chang et al. [23] conducted a randomized controlled study to compare the efficacy and safety of high-dose versus low-dose terlipressin for the treatment of EGVB. They did not find any patient with hyponatremia in both groups. Cavallin et al. [24] conducted a randomized controlled study to compare continuous intravenous infusion versus intravenous bolus terlipressin for type 1 HRS. Similarly, they found that no patient developed hyponatremia in both groups. By comparison, in the present study, we prescribed a relatively short duration of terlipressin and minimized the dosage of terlipressin.

There are several limitations in the present study. First, the patient characteristics were heterogeneous in the Group 1. Second, this was a single-center retrospective cohort study, and the sample size was small. Third, a combination of somatostatin and/or octreotide was also given in some of our patients. Fourth, the time point when we re-checked the serum sodium concentration was defined according to the patients' conditions and disease course. Thus, it was not uniform among patients.

In conclusion, serum sodium concentration reduction can be observed in patients with portal hypertension during terlipressin treatment. However, this phenomenon might not be closely associated with the use of terlipressin. The present study failed to identify any factors associated with serum sodium concentration reduction. Future studies with a larger number of patients should be performed to validate our findings.

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Conflict of interest

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Author contributions

Xinmiao Zhou wrote the protocol, collected the data, performed the statistical analysis, interpreted the data, and drafted the manuscript. Tingxue Song wrote the

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