Original Article

Hyponatremia in Terlipressin-treated patients with gastrointestinal bleeding secondary to portal hypertension

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Abstract

To study the effects of Terlipressin on blood sodium concentrations in individuals with acute portal hypertensive haemorrhage. The observational study was conducted on 34 patients divided in two groups. The two groups were compared for efficacy, safety, overall survival and length of hospital stay. Terlipressin was administered to all of the patients for five days and the observations with respect to the blood sodium level were recorded and analyzed. Twenty-nine male and five female patients were enrolled during the study. All the patients had a Mean Arterial Pressure (MAP) < 90 mmHg and in 30 patients, vital scores such as Child-Turcotte-Pugh or Child-Pugh (CTP) scores with CTP-B of n=10, CTP-C of n=22, and Model for End-stage Liver Disease (MELD) >10 indicated that they had poor liver function. Twenty-two patients exhibited symptoms of moderate to severe ascites. The average sodium levels were 127.6 ± 1 meq/dl and 123.4 ± 0.7 meq/dl on day one and day five, respectively. The mean sodium level drop was noted to be 4.2 ± 0.5 meq/dl which was statistically significant ($p<0.05$) over the five days duration of study. A greater decline was observed in patients with high initial sodium, CTP-A and a lower MELD score. Additionally, any critical neurological or other adverse events were not noticed. Till tapering and discontinuation of Terlipressin, all patients were treated successfully, discontinuation is not required. With better hepatic function, significant blood sodium level reduction was noted. Ascites, low MAP, and other medications were also found to be contributing factors. More Randomized Controlled Trials (RCTs) are necessary to define the precise role of Terlipressin in hyponatremia.

Keywords: Blood Sodium, Hyponatremia, Hypertensive Hemorrhage, Terlipressin Drug.

Introduction

Acute portal hypertensive haemorrhage is a gradually devastating complication of cirrhosis and major reason of mortality in patients with hepatic decompensation.1,2 Portal Hypertension (PH) leads to development of serious complications due to bleeding from oesophageal varices.3 This kind of acute bleeding can be treated by medical and endoscopic treatment, balloon tamponade, placement of fully covered self-expandable metallic stents, Transjugular Intrahepatic Portosystemic Shunt (TIPS) and surgical shunts. Three strategies in combination of vasopressor drugs like Terlipressin, antibiotics and endoscopic therapy have also been found to be effective.4 Recently, Terlipressin with two other vasopressor drugs was reviewed in the treatment of vasodilatory shock owing to its efficacy in cirrhosis, hepatorenal syndrome, and bleeding esophageal varices.5-9

Terlipressin is an abiding synthetic agonist of the natural hormone vasopressin (V1 receptor) with a lesser side effect, that causes splanchnic vasoconstriction and is used in the management of oesophageal and gastric variceal bleeding.10,11 It was found to prevent mortality by 40% by controlling excessive variceal bleeding in 80% cases.12 Machova´ (1995) reported its action on the V2 vasopressin receptors found in the renal collecting ducts, which modulates the vasopressin's antidiuretic effect and found to conserve free water, leads to embellishes hyponatremia in cirrhotic patients.13

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Access this article online

Quick Response Code:

Website: www.pnrjournal.com

DOI: 10.47750/pnr.2022.13.04.183

How to cite this article: D Maindad, Akhil N, Hyponatremia in Terlipressin-treated patients with gastrointestinal bleeding secondary to portal hypertension, J PHARM NEGATIVE RESULTS 2022;13: 1307-1312.

Moreover, there are reports on severe hyponatremia with associated symptoms like seizures has been found in the patients receiving Terlipressin for portal hypertension-induced gastrointestinal haemorrhage.14 The study conducted by Abid et al. has revealed that Terlipressin was as efficient drug as octreotide as an adjuvant therapy for controlling esophageal variceal bleed and in-hospital survival.15 Arora et al. (2020) revealed the superiority of Terlipressin over Noradrenaline in the efficient management of acute kidney injury in acute on chronic liver failure.16 A recent study by Seo et al. (2014) was carried out to compare the efficacy of the three drugs, namely, Somatostatin (SMT), Octreotide, and Terlipressin in the control of acute gastroesophageal variceal haemorrhage.17 Even though no major differences in efficacy was noticed among them, Terlipressin was used at doses lower than recommended. Recently, Magdy et al. (2019) reported that Terlipressin infusion during oncologic Whipple procedure revealed less bleeding and lower rates of requirements of blood transfusion as compared to placebo.18 In another report, Terlipressin was found out to improve pulmonary as well as systemic hemodynamics in stable cirrhotic patients having pulmonary hypertension in comparison to vasoconstrictors which might cause pulmonary pressures to worsen.19

Terlipressin therapy is associated with the rapid reduction in serum sodium level which ultimately may lead to neurological complications and hence monitoring of serum sodium levels in such patients is very decisive in treatment protocols .11,20 Sola et al. (2010) observed rapid reduction in serum sodium concentrations up to 36% in patients with acute variceal bleeding.21 In other report, Gray et al., (2014) studied the effect of Terlipressin on the patient admitted for the treatment of hyponatraemia and the drop of serum sodium from 139 mmol/l to 116 mmol/l after the four days of Terlipressin therapy was observed.11 After, Terlipressin cessation, normal serum sodium level was established within 13 hours with no reported neurological consequences. However, still very few reports are available on the monitoring of serum sodium level after the administration of Terlipressin in patients suffering from acute portal hypertensive haemorrhage. Herein, observational investigation of hyponatremic effect of Terlipressin during pharmacological management of 30+ cases with gastrointestinal bleeding has been presented.

Material and Methods

Study Population

The prospective observational research was undertaken on 34 patients at Bharti Vidyapeeth Medical College Hospital's Intensive Care Unit (ICU), in Western Maharashtra, India during May 2020 and May 2021 after obtaining the written consent from them. In this study, 34 patients were administered Terlipressin (1mg dose) four times a day for pharmacological management of gastrointestinal bleeding caused by cirrhosis-induced portal hypertension. The study was approved by the Institutional Ethics Committee at Bharti Vidyapeeth Medical College, Dhankawadi, Pune, Maharashtra, India. The study was conducted in accordance to the Declaration of Helsinki.

Treatment and Examination

After an essential examination and laboratory screening by Liver Function Test (LFT), Complete Blood Count (CBC), Renal Function Test (RFT), International Normalized Ratio (INR), Electrolytes, etc, all patients were administered intravenous fluid resuscitation with dextrose saline and ringer lactate. Blood products were also administered to them as and when needed. Within 6-12 hours of admission an endoscopic examination was carried out for each patient. Each patient was administered the dose of 1 mg Terlipressin via injection (1 mg / 10 ml of Terlipressin acetate solution) every fourth hour for three days. It was terminated after tapering on fifth day. Serum sodium levels were checked on admission and then after every 24 hours until Terlipressin was discontinued. According to the CP score, MELD score and sodium levels, the patients were separated into sub groups and each group was examined for a drop in blood sodium level and analyzed.

Results

Sodium levels were measured during this study in 34 patients aged 29-56 years (53.4 ± 2.9 years) who displayed an acute portal hypertensive gastrointestinal bleeding and were given Terlipressin as medication. Cirrhosis was the cause of portal hypertension in all patients, and among them, 29 and 5 suffered from alcoholic and non-alcoholic cirrhosis, respectively. On presentation day, all patients displayed symptoms of tachycardia and Mean Arterial Pressure (MAP)s ranging from 60 to 83 mmHg were noted. The patients were anaemic, with haemoglobin levels ranging from 5.4 to 9.1 grams per decilitre and also exhibited thrombocytopenia and coagulopathy (Table 1).

Table 1: Demographic and clinical data of patients before and after administering Terlipressin

Parameter	Mean/number	Range
Age	53.4 ± 2.9 years	29-65 years
Male	30	-
Female	4	-
Pulse rate	107.8 ± 3.3	86-140
MAP	74.0 ± 2.1	60-83
Hemoglobin	5.4-9.1	7.4 ± 0.2
Total count	6854.5 ±1091.6	3400-20300
Platelet count	0.8 ± 0.07	0.49-1.56

Serum creatinine	1 ± 0.1	0.6-1.7
Alcoholic	29	-
Non-alcoholic	5	-
CTP score		
A	2	-
B	10	-
C	22	-
MELD score		
≤10	4	-
11-20	18	-
≥21	12	-
INR	1.82 ± 0.17	1.06-2.69
Ascites		
Mild	12	-
Moderate	5	-
Gross	17	-
Oesophageal varices		
Grade I	2	-
Grade II	10	-
Grade III	22	-
Blood sodium level (meq/dl)		
Day 1	127.6 ±1	121-134
Day 2	126 ±0.9	121-131
Day 3	125±0.8	120-130
Day 4	124.1 ±0.7	120-129
Day 5	123.4±0.7	120-129
Drop in blood sodium level (meq/dl)	4.2±0.5	1-8

Abbreviations: CTP score: Child-Turcotte-Pugh or Child-Pugh score; MELD: Model for End-stage Liver Disease

The patients screened for CP score are classified as CTP A (n=22) with maximum number, followed by CTP B (n=10) and C (n=2), respectively. MELD scores of under 10, 11-20 and more than 21 were reported in 4, 18 and 12 patients, respectively. Mild ascites were detected in 12 individuals, moderate in five and gross in 17 (Table 2).

Table 2: Daily blood sodium level change after administering Terlipressin

Blood sodium level (meq/dl)	**Day 1**	**Day -2**	**Day-3**	**Day -4**	**Day -5**
Mean	127.5	126	125.02	124.0	123.3
SD	3.2	2.7	2.7	2.17	2.15
p-value	< 0.05				

Abbreviations: SD: Standard deviation

Table 3: Daily blood sodium level changes in different CTP score groups and MELD group after administering Terlipressin

Vital Scores	**Day 1**	**Day-2**	**Day-3**	**Day-4**	**Day-5**	**Mean**
CTP Score						
CTP-C	126.18	124.68	123.86	123.13	122.06	3.86
CTP-B	129.6	128.1	126.8	125.5	125.08	4.6
CTP-A	133	130	129	12705	127	6
p-value	< 0.05	<0.05	<0.05	< 0.05	<0.05	-
MELD score						
<10	130.5	128.75	127.75	126.5	125.75	4.75
11-20	127.8	126.2	125.3	124.11	123.5	4.2
>21	126.1	124.6	123.6	123.2	122.2	3.9
p-value	0.06	=0.5	<0.05	=01	<0.05	

Abbreviations: CTP score: Child-Turcotte-Pugh or Child-Pugh score; MELD: Model for End-stage Liver Disease

Table 4: Daily blood sodium levels in different ascites groups after administering Terlipressin

Ascites group	**Day 1**	**Day-2**	**Day-3**	**Day-4**	**Day-5**	**Mean**
Mild	128.8	127.1	126.1	124.9	124	4.8

Moderate	128.6	126.4	125.8	125.2	124.6	4
Gross	126.6	125.3	124.2	123.3	122.6	3.9
p-value	0.1	1.3	0.13	0.1	0.1	0.8

Varices in the oesophagus were graded as one, two and three with three being the most severe (Table 3). There were 22 patients with grade three varices, ten with grade two varices and two with grade one varices. Endoscopy was performed on all patients within 6-12 hours, and sufficient haemostasis was established. Administration of Terlipressin was tapered after day three and completely stopped on the fifth day. None of the patients experienced significant hyponatremia-related complications, necessitating Terlipressin cessation.

Blood sodium levels less than 135 meq/dl were detected in all the patients on the presentation day before commencing Terlipressin. Blood sodium levels in the ranges of 135-131 meq/dl, 126-130 meq/dl and less than 125 meq/dl were observed in 4, 22 and 8 patients, respectively, with the mean of 127.6 ±1 meq/dl (Table 4). On the second day, 28 individuals exhibited blood sodium level reductions ranging from 1-4 meq/dl (mean 1.6 meq/dl). The sodium concentration in the blood varied from 121 to 131 meq/dl (mean 126 ± 0.9 meq/dl). On the third day, blood sodium levels declined between 1-3 meq/dl (mean1.0 meq/dl) in 25 patents. The sodium level in blood was noted to be in the range of 120-130 meq/dl (mean 125 ± 0.8 meq/dl). Sodium levels in 25 patients dropped by 1-2 meq/dl (mean 0.9 meq/dl) on the fourth day, with sodium levels ranging from 120-129 meq/dl (124.1± 0.7 meq/dl). On the final (fifth) day, sodium levels in 21 individuals declined by 1-2 meq/dl (mean drop 0.7 meq/dl)). The sodium levels were in the 120-129 meq/dl (123.4 ± 0.7 meq/dl) range. Thus, within five days, all patients exhibited blood sodium level decline ranging from 1 to 8 meq/dl, with a mean reduction of 4.2 ± 0.5 meq/dl.

The average sodium level was 127.5 ± 3.2 meq/dl on the first day. 126 ± 2.6 meq/dl on day 2, 125.02 ± 2.7 meq/dl on day 3, 124 ± 2.17 meq/dl on day 4, and 123.3 ± 2.15 meq/dl on day 5. In five days, sodium levels dropped significantly, with a p-value of < 0.05 (Table 2).

On the presentation day, greater blood sodium levels were detected in CTP class A patients than CTP classes B and C (133 vs. 129.6 and 126.1 meq/dl, respectively). However, CTP A patients displayed a more significant decline in blood sodium levels over five days than CTP B and CTP C patients (6 vs.4.6 and 3.86 meq/dl, respectively). The patients belonging to CTP B group showed a more significant blood sodium decrease rate than the CTP A group ($p<0.05$). Nevertheless, owing to the small number of patients in the CTP A group, a comparison with the other groups was not feasible.

Patients with MELD score > 21 reported blood sodium decrease of 3.9 meq/dl, while patients with MELD score in the range of 11-20 were observed with a drop in blood sodium level of 4.2 meq/dl. Patients with MELD ≤10 have registered a sodium drop of 4.75 meq/dl. Thus, patients with a higher MELD score showed a lower reduction in sodium levels than those with a lower MELD score (Table 3); however, this finding was statistically insignificant (with p=0.8).

Blood sodium level decline in patients with mild ascites was 4.6 meq/dl, and in patients with moderate and in gross ascites, the decrease with registered to be 4 meq/dl and 3.6 meq/dl. However, this difference was statistically insignificant (Table 4). Twenty patients (58.82%) registered blood sodium level drop of >4 meq/dl and 14 patients (41.17%) reported the drop in blood sodium level of < 4 meq/dl.

Discussion

Throughout the five-day observation period, all individuals treated with Terlipressin experienced a decrease in salt (sodium) levels in blood gradually on each passing day. It ranged from a minor to a significant decline, from 2 to 8 meq/dl, with a maximum loss of 4 meq/dl in one day (Fig. 1).

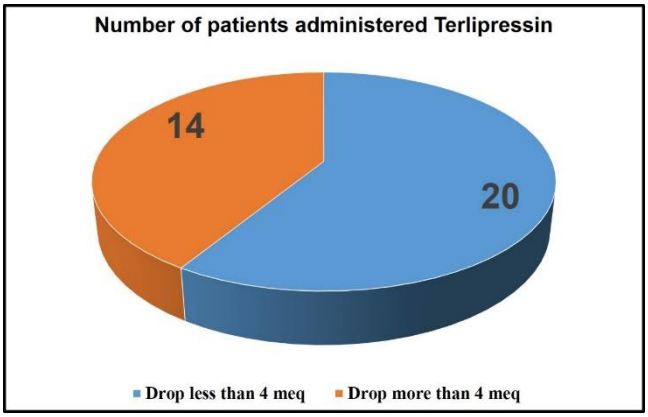

Figure 1: Number of patients administered Terlipressin and drop in blood sodium level

In retrospective research by Sola et al. (2010), 67 percent of patients treated with Terlipressin were reported with reduction in blood sodium levels.21 In the same study, neurological symptoms were observed in 14% of patients with a sodium decline of more than 10 meq/dl. Our investigation showed no neurological manifestation of hyponatremia, which might be due to a smaller sodium level decline (max drop was 8 meq/dl over five days). It is difficult to quantitatively attribute the contribution of Terlipressin for the drop in blood sodium levels. The sodium level decline was affected by a variety of factors. Mild to severe ascites

was present in 22 individuals (64.70%) which might play a part in the onset of dilutional hyponatremia. In such cases, the large volume of resuscitation fluid leads to third-space fluid build-up that results in dilutional hyponatremia. Although the acute renal injury was noted in just four people, it might contribute to hyponatremia. Such patients reported a MAP of 74.0 ± 2.1 mmhg, which might have activated the renin-angiotensin system and contributed to hyponatremia. These secondary causes of hyponatremia in patients can exacerbate hyponatremia induced by Terlipressin.22

Terlipressin studies in patients suffering from Hepatorenal Syndrome (HRS) reported reduction in initial blood sodium levels.23 Such drop was ascribed to the role of low MAP and activation of the renin-angiotensin system in hyponatremia. Only 10% of HRS patients displayed a drop in blood sodium level in their report. In our clinical observations of the present report, the decline in sodium levels was uneven; in some individuals, the drop was more considerable, while in others, it was insignificant. Blood sodium levels did not change every day consistently in all patients over the five-day observations. It implies that multiple elements play a role in hyponatremia observed in these patients.

We noted that the higher the starting sodium level, the more significant the blood sodium level drop in patients. Patients in the CTP- A group and low MELD score reported relatively higher decline in blood sodium level. Many compensatory mechanisms are active in patients with high MELD and CTP-B, CTP-C scores due to persistent low blood sodium levels, leading to a lesser drop. In this context, more such studies and allied testing are required for confirmation of mechanism of action of Terlipressin.

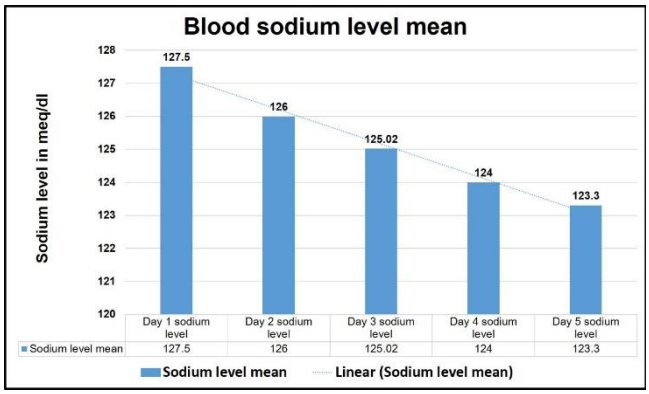

Figure 2: Daily drop in blood sodium level (mean) after Terlipressin administration in patients

Hyponatremia was reported to worsen when the period of therapy lengthens in a study by Bruha et al. (2009).24 They reported the decline in blood sodium level from 129.85 ± 9.4 meq/dl on fifth day to 121.4 ± 8.1 meq/dl on 10th day.24 Contrary to this, we observed reduction in blood sodium levels with increase in treatment time (Fig. 2). Additionally, we did not observe a recovery of blood sodium levels after termination of Terlipressin treatment.

Our investigation revealed Terlipressin-induced hyponatremia in all 34(100%) patients, although it ranged from 10-70% in other studies. Though considerable research on the effect of terlipressin on acute variceal gastrointestinal bleeding has been reported, its hyponatremic potential has been scarcely highlighted.25

If Terlipressin and Vasopressin are compared, though Vasopressin treatment reported lesser hyponatremia (5 vs. 3 instances), less than 10% of patients showed such adverse event; thus, it may not be considered significant.14 There are very few reports on neurological side effects and seizures in patients after treatment by Terlipressin.11 Hyponatremia in Terlipressin is reported to be reversible after discontinuation and there is no need for treatment without neurological symptoms.24 In the similar line, no notable neurological complications associated with hyponatremia were observed in our investigation.

Discontinuation and re-challenge of Terlipressin confirmed hyponatremia in users which also supports the role of Terlipressin in controlling serum sodium level.26 However, higher starting sodium plasma levels, younger age and maintained hepatic functioning are independent and higher risk factors for hyponatremia development (indicated by low CTP and MELD scores).27,28

Limitations of the study

Our study is limited in scope as just 34 patients were involved in the investigation. Their further categorization into subgroups based on CP classes and MELD scores drops their numbers in each category relatively lesser. Consequently, statistical values are inconclusive. Additionally, a controlled group of patients with non-Terlipressin pharmacotherapy was not available in the present study. Nevertheless, other reported studies on Terlipressin-induced hyponatremia in acute gastrointestinal bleeding exhibited similar limitations with findings of our study. RCTs with larger numbers of patients are also needed to accurately confer the role of Terlipressin-induced hyponatremia in cirrhotic patients.

Conclusion

We studied the effects of Terlipressin on blood sodium concentrations in 34 patients with acute portal hypertensive haemorrhage which were divided into four groups. With better hepatic function, significant blood sodium level reduction was noted after the administration of Terlipressin. Ascites, low mean arterial pressure, and other medications were also found to be contributing factors. More RCTs are essential to ascertain the contribution of Terlipressin in hyponatremia.

Acknowledgement

The authors acknowledge the support received from the management of BVDU, Pune and from the Medical College of BVDU, Pune.

Funding sources

No funding source.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Sass DA, Chopra KB. Portal hypertension and variceal hemorrhage. Med Clin North Am 2009; 93(4):837-853.
2. Garcia-Tsao, G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007;46(3):922-938.
3. Biecker E. Portal hypertension and gastrointestinal bleeding: diagnosis, prevention and management. World J Gastroenterol 2013;19(31):5035-5050.
4. Bañares R, Albillos A, Rincón D, Alonso S, González M, Ruiz-del-Arbol L, Salcedo M, Molinero LM. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. Hepatology. 2002; 35:609-615.
5. Rodriguez R, Cucci M, Kane S. Novel vasopressors in the treatment of vasodilatory shock: A systematic review of Angiotensin II, Selepressin, and Terlipressin. J. Intensive Care Med 2018;1-11.
6. Boyer TD, Sanyal AJ, Wong W, Frederick RT, Lake JR, O'leary JG, et al. Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with cirrhosis and hepatorenal syndrome type 1. Gastroenterology 2016; 150:1579-1589.
7. Morelli A, Ertmer C, Pietropaoli P, Westphal M. Terlipressin: a promising vasoactive agent in hemodynamic support of septic shock. Expert Opin Pharmacother 2009; 10(15):2569-2575.
8. Rajekar H, Chawla Y. Terlipressin in hepatorenal syndrome: Evidence for present indications. J Gastroenterol Hepatol 2011; 26;109–114.
9. Mahdy MM, Abbas MS, Kamel EZ, Mostafa MF, Herdan R, Hassan SA, et al. Effects of terlipressin infusion during hepatobiliary surgery on systemic and splanchnic haemodynamics, renal function and blood loss: a double-blind, randomized clinical trial. BMC Anesthesiol 2019; 19:106.
10. Freeman JG, Cobden I, Lishman AH, Record CO. Controlled trial of terlipressin ("Glypressin") versus vasopressin in the early treatment of oesophageal varices. Lancet 1982; 2(8289): 66-68.
11. Gray R, Kilic J, Anderson P. Terlipressin-induced hyponatraemia. Crit Care. 2014;18: P159.
12. Feu F, Ruiz del Arbol L, Banares R, Planas R, Bosch J. Double-blind randomized controlled trial comparing terlipressin and somatostatin for acute variceal hemorrhage. variceal bleeding study group. Gastroenterology 1996; 111:1291–1299.
13. Machova´ A. Antidiuretic activity of terlipressin (triglycyl-lysine vasopressin) -- role of pressure natriuresis. Physiol Res 1992; 41:121-127.
14. Hyun JJ, Seo YS, Gyun K, Terlipressin-induced hyponatremic seizure. Scand J Gastroenterol 2010; 45(4):501-504.
15. Abid S, Jafri W, Hamid S, Salih M, Azam Z, Khalid M, et al. Terlipressin vs. octreotide in bleeding esophageal varices as an adjuvant therapy with endoscopic band ligation: a randomized double-blind placebo-controlled trial. Am J Gastroenterol 2009; 104: 617-623.
16. Arora V, Maiwall R, Rajan V, Jindal A, Shasthry SM, Kumar G, et al. Terlipressin is superior to noradrenaline in the management of acute kidney injury in acute on chronic liver failure. Hepatology, 2020;71(2):600-610.
17. Seo YS, Park SY, Kim MY, Kim JH, Park JY, Yim HJ, et al. Lack of difference among Terlipressin, Somatostatin, and Octreotide in the control of acute gastroesophageal variceal hemorrhage. Hepatology 2014; 60:954-963.
18. Magdy MM, Osama IA, Jehan SA, Mostafa AS. Terlipressin infusion during Whipple procedure: effect on blood loss and transfusion needs – a randomized clinical trial. J Current Med Res Pract 2019; 4:137-143.
19. Kalambokis GN, Pappas K, Tsianos EV. Terlipressin improves pulmonary pressures in cirrhotic patients with pulmonary hypertension and variceal bleeding or hepatorenal syndrome. Hepatobiliary Pancreat Dis Int 2012;11(4):434-437.
20. Zaki SA. Terlipressin-induced hyponatremic seizure in a child. Indian J Pharmacol 2013; 45(4): 403-404.
21. Sola E, Lens S, Guevara M, Martin-Llahi M, Fagundes C, Pereira G, et al. Hyponatremia in patients treated with terlipressin for severe gastrointestinal bleeding due to portal hypertension. Hepatology 2010; 52:1783-1790.
22. Ackermann D. Treatment of Ascites, hyponatremia and hepatorenal syndrome in liver cirrhosis. Ther Umsch 2009; 66:747-751.
23. Nazar A, Pereira GH, Guevara M, Martin-Llahi M, Pepin MN, Marinelli M, et al. Predictors of response to therapy with terlipressin and albumin in patients with cirrhosis and type 1 hepatorenal syndrome. Hepatology 2010; 51:219-226.
24. Bruha R, Marecek Z, Prochazka V, Lata J, Spicak J, Erhmann J, et al. Double-blind randomized multicenter study comparing the efficacy and safety of 10-day to 5-day terlipressin treatment of bleeding esophageal varices. Hepatogastroenterology 2009; 56:390-394.
25. Krag A, Hobolth L, Moller S, Bendtsen F. Hyponatraemia during terlipressin therapy. Gut 2010; 59: 417–418.
26. Šíma M, Pokorný M, Paďour F, Slanar O, et al. Terlipressin induced severe hyponatremia. Prague Med Rep 2016; 117:68-72.
27. Kang YJ, Bae EJ, Hwang K, Jeon DH, Jang HN, Cho HS, et al. Initial serum sodium concentration determines the decrease in sodium level after terlipressin administration in patients with liver cirrhosis. Springerplus 2013; 2:519
28. Yim SY, Seo YS, Jung CH, Kim TH, Kim ES, Keum B, et al. Risk factors for developing hyponatremia during terlipressin treatment: a retrospective analysis in variceal bleeding. J Clin Gastroenterol 2015; 49(7):607-612.