

**Research Article**

## Hyponatremia induced by terlipressin: a descriptive case series study

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### ABSTRACT

**Objective:** To assess the hyponatremia induced by Terlipressin in cases of acute variceal bleeding.

**Materials & Methods:** This descriptive case series study was consisted on 100 patients with acute variceal bleeding presenting at DHQ Hospital, Vehari from June 2017 to December 2017. Hyponatremia induced by Terlipressin was assessed.

**Results:** Age range was from 20 to 60 years with mean age of  $45.78 \pm 8.43$  years. Out of 100 patients, terlipressin induced hyponatremia was noted in 37 (37%) patients. Total 45 (45%) patients belonged to age group 20-40 years and Terlipressin induced Hyponatremia was noted in 17 (37.78%) patients. Total 55 (55%) patients belonged to age group 41-60 years and Terlipressin induced Hyponatremia was noted in 20 (36.37%) patients.

**Conclusion:** Results of this study showing a high rate of terlipressin induced hyponatremia. There was not association of terlipressin induced hyponatremia with age and gender was detected.

**Keywords:** Vasoactive drugs, sodium levels, upper GI bleeding, hyponatremia, terlipressin

### INTRODUCTION

Gastro-esophageal varices are present in 40–60% of patients with cirrhosis; bleeding occurs in 25–35% of patients and account for 80–90% of bleeding episodes in these patients.<sup>1</sup> Variceal bleeding is a severe complication of portal hypertension, causing 70% of all upper gastrointestinal bleeding episodes in patients with liver cirrhosis.<sup>2,3</sup> Thus a variceal origin should be suspected in any cirrhotic patient with acute upper gastrointestinal bleeding. Diagnosis is established at emergency endoscopy on the basis of observing one of the following: active bleeding from a varix (observation of blood spurting or oozing from the varix), white nipple or clot adherent to a varix, and presence of varices without other potential sources of bleeding.<sup>4</sup>

Over the last decade, there have been numerous advances in the management of variceal

bleeding. Many guidelines have been published to suggest the evidence based appropriate management of patients with variceal bleeding.<sup>5</sup> Endoscopic intervention along with pharmacologic treatment achieves control of bleeding in nearly 70 – 80 % of episodes of variceal bleeding.<sup>6</sup> Endoscopic treatment modalities available include variceal ligation and injections sclerotherapy. Endoscopic sclerotherapy is based on the concept that bleeding from varices is halted by thrombosis of the bleeding varix by intravariceal or paravariceal injection of a sclerosant. The most commonly used sclerosants are sodium tetradecyl sulphate (thrombovar) and ethanolamine oleate.<sup>7</sup>

Terlipressin was introduced some decades ago as an alternative to vasopressin, which is only sparsely used in cirrhosis due to an unfavorable

safety profile. It is now standard therapy in bleeding esophageal varices in the countries where it is available, because it is the only vasoactive drug that improves survival.<sup>8</sup> Terlipressin is a vasopressin receptor agonist with predominant effect on the vasopressin-1 receptors, which is responsible for the haemodynamic effects. But, terlipressin also has affinity to vasopressin-2 receptors, which are located in the collecting ducts of the kidneys and induce water retention through insertion of the water canal aquaporin-2. Terlipressin improves renal function and induces natriuresis but decreases excretion of solute-free water, which can explain the development of hyponatraemia.<sup>10</sup> Sola et al<sup>18</sup> in his study has observed that 36% patients developed hyponatremia i.e. decrease in serum sodium >10 mEq/L, after terlipressin therapy.

#### OPERATIONAL DEFINITIONS:

**Active variceal bleeding:** was defined as active blood from varices or cherry red spots on varices and no other hemorrhagic source was found in the stomach and duodenum on endoscopy.

**Terlipressin induced Hyponatremia:** was deemed as positive if there was reduction in serum sodium levels of  $\geq 10$  mEq/L from baseline, during terlipressin therapy (on day 1, 2 & 3 of terlipressin therapy) and final outcome was measured on 3<sup>rd</sup> day.

#### MATERIAL AND METHODS

This descriptive case series study consisted of 100 patients with acute variceal bleeding presenting at DHQ Hospital, Vehari from June 2017 to December 2017. Total 100 patients with acute variceal bleeding due to portal hypertension, 20-60 years of age, either male or female were selected for this study. Patients with bleeding due to other causes, patients with hepatocellular carcinoma, patients with other causes of hyponatremia i.e. nephritic syndrome, hypothyroidism, severe diarrhea, Addison disease etc., patients with cardiovascular disease or renal failure, patients with serum sodium levels  $\leq 135$  mEq/L on presentation, pregnant patients,

patients with hypersensitivity to terlipressin and patients not willing to be included in the study were excluded.

History and physical examination, all laboratory investigations especially serum sodium levels were done. Then, after all initial resuscitative measures, terlipressin therapy was started in each patient at a dose of 2 mg every 4 hours for the first 24 hours, and then 1 mg every 4 hours for up to 3 days. During terlipressin therapy, serum sodium levels were monitored and checked twice a day for any reduction in serum sodium levels > 10 mEq/L (hyponatremia) from baseline and final outcome was noted at the end of 3<sup>rd</sup> day. This all data was recorded on a specially designed proforma which contained two parts. Part 1<sup>st</sup> included the patient's bio-data while part 2<sup>nd</sup> contained the study variables.

Collected data was analyzed through computer software SPSS 20.0. Mean and standard deviation was calculated for quantitative variables i.e. age and serum sodium levels. Frequency and percentage was calculated for qualitative variables i.e. gender and terlipressin induced hyponatremia (yes/no). Effect modifiers like age and gender were controlled through stratification and post-stratification chi square was applied to see their effect on outcome. P-value  $\leq 0.05$  was considered as significant.

#### RESULTS

Total 100 patients of acute variceal bleeding were selected for this study. Age range was from 20 to 60 years with mean age of  $45.78 \pm 8.43$  years. Out of 100 patients, terlipressin induced hyponatremia was noted in 37 (37%) patients.

Patients were divided into two age groups i.e. age group 20-40 years and age group 41-60 years. Total 45 (45%) patients belonged to age group 20-40 years and Terlipressin induced Hyponatremia was noted in 17 (37.78%) patients. Total 55 (55%) patients belonged to age group 41-60 years and Terlipressin induced Hyponatremia was noted in 20 (36.37%) patients. Statistically insignificant association between Terlipressin induced

Hyponatremia and age was noted with p value 1.00. (Table 1)

Out of 100 patients, male patients were 58 (58%) and Terlipressin induced Hyponatremia was observed in 20 (34.48%) male patients. Out of 42 (42%) female patients, Terlipressin induced

Hyponatremia was observed in 17 (40.48%) female patients. But insignificant association between gender and Terlipressin induced Hyponatremia was observed with p value 0.6751. (Table 2)

**Table 1:** Relation of age with hyponatremia

Age (years)	Terlipressin induced Hyponatremia		Total (%)	p-value
	Yes (%)	No (%)		
20-40	17 (37.78)	28 (62.22)	45 (45)	1.00
41-60	20 (36.37)	35 (63.63)	55 (55)	
Total	37 (37)	63 (63)	100	

**Table 2:** Relation of Gender with terlipressin induced hyponatremia

Gender	Terlipressin induced Hyponatremia		Total (%)	p-value
	Yes (%)	No (%)		
Male	20 (34.48)	38 (65.52)	58 (58)	0.6751
Female	17 (40.48)	25 (59.52)	42 (42)	
Total	37 (37)	63 (63)	100	

## DISCUSSION

Terlipressin is commonly used to treat acute variceal bleeding. Terlipressin, a synthetic vasopressin analogue with fewer side-effects and a longer half-life than vasopressin, is effective in controlling acute variceal bleeding.<sup>11</sup> Terlipressin is administered as IV injections of 2mg bolus and 1mg every four to six hours for 2-5 days. A meta-analysis demonstrated that terlipressin was associated with a 34% relative risk reduction in mortality compared to placebo.<sup>11</sup>

Terlipressin significantly improved the rate of control of bleeding and survival. This is the only drug that has been directly shown to improve mortality in variceal bleeding.<sup>12</sup> Terlipressin is as effective as any other effective therapy, including endoscopic injection sclerotherapy, and is safer than vasopressin + nitroglycerin and endoscopic injection sclerotherapy.<sup>13</sup> The overall efficacy of terlipressin in controlling acute variceal bleeding

at 48 hours is 75 to 80% across trials<sup>95</sup> and 67% at 5 days.<sup>13</sup>

Age range was from 20 to 60 years with mean age of  $45.78 \pm 8.43$  years. Out of 100 patients, terlipressin induced hyponatremia was noted in 37 (37%) patients. Azam Zet al<sup>14</sup> and Akhtar N et al<sup>15</sup> reported mean age as 47 years and 45 years which is comparable with our study. Shaikh WM et al<sup>100</sup> reported mean age as 41 years. Many previous studies have shown much higher mean age i.e. above 50 years, as compared to our study.<sup>1,8,9</sup>

Out of 100 patients, male patients were 58 (58%) and Terlipressin induced Hyponatremia was observed in 20 (34.48%) male patients. Out of 42 (42%) female patients, Terlipressin induced Hyponatremia was observed in 17 (40.48%) female patients. But insignificant association between gender and Terlipressin induced Hyponatremia was observed with p value 0.6751. This male predominance was also found in many previous studies.<sup>14,16</sup>

Sola et al<sup>10</sup> in his study examine the effects of terlipressin on serum sodium concentration in 58 patients with acute portal-hypertensive bleeding and found decrease in serum sodium from  $134.9 \pm 6.6$  mEq/L to  $130.5 \pm 7.7$  mEq/L ( $P = 0.002$ ). A reduction of sodium in the blood was found in 67% of patients with 31% having a moderate decrease (5-10 mEq/L) and 36% experiencing a marked decrease in serum sodium (greater than 10mEq/L). Douriez E et al<sup>17</sup> in 1993 in his study has observed severe hyponatremia after repeated administration of terlipressin. Feu F et al<sup>18</sup> in his study reported only 6.25% patients of hyponatremia among 80 patients treated with terlipressin for acute variceal bleeding. Escorsella et al<sup>13</sup> observed four cases of hyponatraemia in 105 patients treated with Terlipressin compared with no cases in the sclerotherapy group.

## CONCLUSION

Results of this study showing a high rate of terlipressin induced hyponatremia. There was not association of terlipressin induced hyponatremia with age and gender was detected.

## REFERENCES

1. Majid S, Azam Z, Shah HA, Salih M, Hamid S, Abid S, et al. Factors determining the clinical outcome of acute variceal bleed in cirrhotic patients. *Indian J Gastroenterol.* 2009;28(3):93–5.
2. Garcia-Pagan JC, Reverter E, Abraldes JG, Bosch J. Acute variceal bleeding. *SeminRespirCrit Care Med.* 2012;33:46–54.
3. deFranchis R, Faculty BV. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepato.l* 2010;53(4):762–68.
4. D'Amico G. Esophageal varices: from appearance to rupture; natural history and prognostic indicators. In: Groszmann RJ, Bosch J., eds. *Portal Hypertension in the 21st Century.* Dordrecht: Kluwer Academic. 2004:147–54.
5. Farooqi JI, Jafri SMW, Haq N, Niaz SK, Hamid S, Abbas Z, et al. Management of variceal bleeding: PSG guidelines 2006. *J Pak Med Assoc.* 2007;57(10):505-11.
6. Abid S, Jafri W, Hamid S, Salih M, Azam Z, Mumtaz K, 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;104:617–23.
7. Lo GH, Lai KH, Cheng JS. A prospective, randomized trial of sclerotherapy versus ligation in the management of bleeding esophageal varices. *Hepatology.* 1995;22(2):466–71.
8. Hyun JJ, Seo YS, Lee KG, Keum B, Yim HJ, Jeon YT. Terlipressin-induced hyponatremic seizure. *Scand J Gastroenterol.* 2010;45(4):501-4.
9. Krag A, Møller S, Bendtsen F. Hyponatremia in patients treated with terlipressin: mechanisms and implications for clinical practice. *Hepatol.* 2011;53(1):368-9.
10. 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. *Hepatol.* 2010;52(5):1783-90.
11. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane Database Syst Rev.* 2003;(1):CD002147.
12. Ioannou GN, Doust J, Rockey DC. Systematic review: terlipressin in acute oesophagealvaricealhaemorrhage. *Aliment PharmacolTher.* 2003;17(1):53–64.
13. Escorsell A, Ruiz del Arbol L, Planas R, Albillos A, Banares R, Cales P, et al. Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. *Hepatology* 2000;32:471-476.
14. Azam Z, Hamid S, Jafri W, Salih M, Abbas

- Z, Abid S, et al. Short course adjuvant terlipressin in acute variceal bleeding: a randomized double blind dummy controlled trial. *J Hepatol.* 2012 Apr;56(4):819-24.
15. Akhtar N, Zuberi BF, Hasan SR, Kumar R, Afsar S. Determination of correlation of Adjusted Blood Requirement Index with outcome in patients presenting with acute variceal bleeding. *World J Gastroenterol.* 2009;15(19):2372-75.
  16. Shaikh WM, Shaikh SM, Shaikh MA, Solangi GA, Zuberi BF. A comparative study of efficacy of octreotide and sclerotherapy in variceal bleeding. *JCPSP.* 2002;12(11):677-81.
  17. Douriez E, Mollard P, Laval C, Albengres E, Laporte JP, Tillement JP. Severe hyponatremia after repeated administration of terlipressin. *Therapie.* 1993 Sep-Oct;48(5):518-9.
  18. Feu F, Ruiz del Arbol L, Bañares R, Planas R, Bosch J. Double-blind randomized controlled trial comparing terlipressin and somatostatin for acute variceal hemorrhage. *Variceal Bleeding Study Group. Gastroenterology.* 1996 Nov;111(5):1291-99.