CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
http://doi.org/10.5281/zenodo.3526514

Available online at: http://www.iajps.com *Research Article*

AN ASSESSMENT OF HYPONATREMIA IN CASES OF ACUTE VARICEAL BLEEDING TREATED WITH TERLIPRESSIN

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Article Received: September 2019 **Accepted:** October 2019 **Published:** November 2019

Abstract:

Objective: *To assess the hyponatremia in cases of acute variceal bleeding treated with terlipressin.*

Materials & Methods: *This descriptive case series was conducted at Department of Pharmacology, Lahore Medical and Dental College Lahore from April 2018 to October 2018 over the period of 6 months. 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. Terlipressin induced hyponatremia was assessed.*

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 ± 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.*

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Please cite this article in press Talha Laique et al., ***An Assessment of Hyponatremia in Cases of Acute Variceal Bleeding Treated with Terlipressin****., Indo Am. J. P. Sci, 2019; 06(11).*

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. [1] Variceal bleeding is a severe complication of portal hypertension, causing 70% of all upper gastrointestinal bleeding episodes in patients with liver cirrhosis. [2,3] 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. [4]

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. [5] Endoscopic intervention along with pharmacologic treatment achieves control of bleeding in nearly 70 – 80 % of episodes of variceal bleeding.[6] Endoscopic treatment modalities available include variceal ligation and injection 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. [7]

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. [8] 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. [10] Sola et al[18] in his study has observed that 36% patients developed hyponatremia i.e. decrease in serum sodium >10 mEq/L, after terlipressin therapy.

MATERIAL AND METHODS:

This descriptive case series was conducted at Department of Pharmacology, Lahore Medical and Dental College Lahore from April 2018 to October 2018 over the period of 6 months. 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 ≤ 135mEq/L on presentation, pregnant patients, patients with hypersensitivity to terlipressin and patients not willing to be included in the study were excluded.

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 ≥10 mEq/L from baseline, during terlipressin therapy (on day 1, 2 & 3 of terlipressin therapy) and final outcome was measured on 3rd day.

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 3rd day. This all data was recorded on a specially designed proforma which contained two parts. Part 1st included the patient's bio-data while part 2nd 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 ≤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 ± 8.43 years. Out of 100 patients, terlipressin induced hyponatremia was noted in 37 (37%) patients.

Patients were divided into two age group 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 vlaue 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. [11] 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. [11]

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. [12] Terlipressin is as effective as any other effective therapy, including endoscopic injection sclerotherapy, and is safer than vasopressin + nitroglycerin and endoscopic injection sclerotherapy. [13] The overall efficacy of terlipressin in controlling acute variceal bleeding at 48 hours is 75 to 80% across trials[95] and 67% at 5 days. [13]

Age range was from 20 to 60 years with mean age of 45.78 ± 8.43 years. Out of 100 patients, terlipressin induced hyponatremia was noted in 37 (37%) patients. Azam Z et al [14] and Akhtar N et al [15] reported mean age as 47 years and 45 years which is comparable with our study. Shaikh WM et al[100] 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. [1,8,9]

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 vlaue 0.6751. This male predominance was also found in many previous studies. [14,16]

Sola et al [10] 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 ± 6.6 mEq/L to 130.5 ± 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 [17] in 1993 in his study has observed severe hyponatremia after repeated administration of terlipressin. Feu F et al [18] in his study reported only 6.25% patients of hyponatremia among 80 patients treated with terlipressin for acute variceal bleeding. Escorsell A et al [13] 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.

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