

Frequency of Terlipressin Induced Hyponatremia in Patients of Variceal Bleeding

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ABSTRACT

Aim: To determine frequency of terlipressin induced hyponatremia in pts with acute variceal bleeding.

Methods: A total of 139 patients with acute variceal bleeding of age 20-60 years and both genders were included. Patients with renal failure, hepatocellular carcinoma and hypersensitivity to Terlipressin were excluded. After 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 1mg 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 >10mEq/L from baseline and final outcome was noted at the end of 3rd day.

Results: Terlipressin induced Hyponatremia was found in 56(40.3%) patients, whereas there was no hyponatremia in 83(59.7%) patients.

Conclusion: Frequency of terlipressin induced hyponatremia in patients with acute variceal bleeding is very high(40.3%),so regular monitoring of serum sodium levels should be done during terlipressin therapy.

Keywords: Upper GI bleeding, vasoactive drugs, sodium levels.

INTRODUCTION

Variceal bleeding is a severe complication of portal hypertension, causing 70% of all upper gastrointestinal bleeding episodes in patients with liver cirrhosis^{1,2}. 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 bleeding³.

Within the last few decades mortality in relation to bleeding esophageal varices has decreased from 40% to 15%, with the introduction of new treatment modalities including vasoactive drugs such as vasopressin and terlipressin⁴. Vasoactive drugs have been shown to control acute variceal bleeding in about 80% of patients⁵. Vasoactive therapy can be used empirically when variceal bleeding seems likely on clinical grounds. The current recommendation is to start a vasoactive drug as early as possible from the time of admission or even upon the patient's transfer to the hospital⁶.

METHODOLOGY

A total of 139 patients who were admitted to the department of Medicine, BVH, Bahawalpur from May

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2014 to November 2014 after fulfilling the criteria were selected. All patients either male or female with acute variceal bleeding due to portal hypertension having age 20 to 60 years were included in this study. 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.

Patients with hepatocellular carcinoma, nephritic syndrome, hypothyroidism, severe diarrhea, Addison disease, patients with cardiovascular disease or renal failure, patients with serum sodium levels \leq 135mEq/L on presentation, pregnant patients and patients with hypersensitivity to terlipressin were excluded from the study. After taking informed written consent and relevant history and physical examination, all laboratory investigations especially serum sodium levels were done. Then, after 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 >10mEq/L (hyponatremia) from baseline and final outcome was noted at the end of 3rd day. Terlipressin induced Hyponatremia was 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). All the data was noted in pre-designed proforma. All the data were entered in SPSS version 16 and analyzed.

RESULTS

Detail of results is given in tables 1, 2, 3. Out of the 139 patients, 88 (63.3%) were male and 51(36.7%) were females with ratio of 1.7:1 . No significant association was found between Terlipressin induced Hyponatremia and gender (P value 0.871). Pre-therapy, post-therapy and mean reduction in serum sodium levels are shown in Table 3.

Fig 1: Terlipressin induced hyponatremia

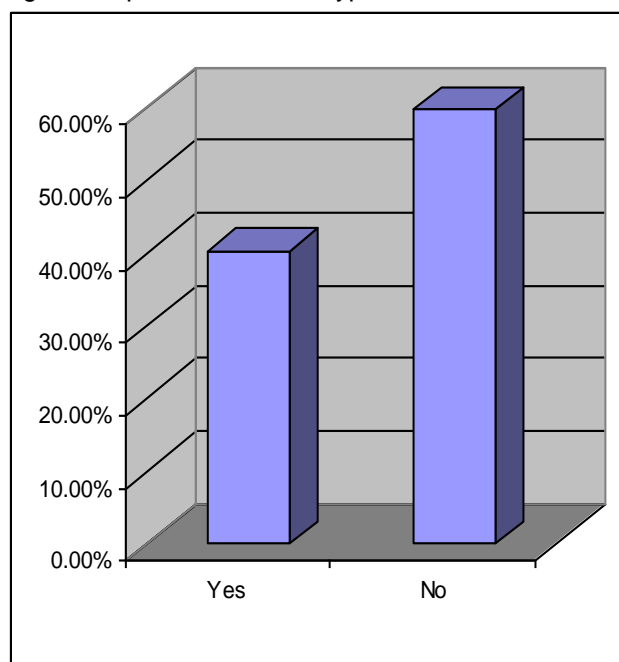


Table 1: Stratification of age

Age (yrs)	Terlipressin induced Hyponatremia		Total
	Yes	No	
20-30	05(38.5%)	08(61.5%)	13(9.4%)
31-40	15(44.1%)	19(55.9%)	34(24.5%)
41-50	17(39.5%)	26(60.5%)	43(30.9%)
51-60	19(38.8%)	30(61.2%)	49(35.4%)

P-value:0.963

Table 2: Stratification of gender

Gender	Terlipressin induced Hyponatremia		Total
	Yes	No	
Male	35(39.8%)	53(60.2%)	88(63.3%)
Female	21(41.2%)	30(58.8%)	51(36.7%)

P-value: 0.871

Table 3: Serum sodium levels.

	Mean±SD
Pre-therapy Serum sodium (mEq/L)	136.87±9.68
Post-therapy Serum sodium (mEq/L)	124.15±11.13
Reduction Serum sodium (mEq/L)	11.03±7.71

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. A meta-analysis demonstrated that terlipressin was associated with a 34% relative risk reduction in mortality compared to placebo⁹. In acute variceal bleeding, terlipressin may have an added advantage as it can potentially reverse hepato renal syndrome. In addition, terlipressin has been shown to have a more sustained haemodynamic effect compared to treat with octreotide¹⁰.

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. Terlipressin is as effective as any other effective therapy, including endoscopic injection sclerotherapy, and is safer than vasopressin + nitroglycerin and endoscopic injection sclerotherapy. The overall efficacy of terlipressin in controlling acute variceal bleeding at 48 hours is 75%-80% across trials and 67% at 5 days.^{11,12} Clinical studies have consistently shown less frequent and severe side effects with terlipressin than with vasopressin (even if associated with nitroglycerin). The most common side effect of this drug is abdominal pain. Serious side effects such as peripheral, intestinal, or myocardial ischemia occur in < 3% of the patients¹² and reverse after drug withdrawal.

This study was conducted to determine the frequency of terlipressin induced hyponatremia in patients with acute variceal bleeding. The mean age in this study was 46.4±7.8 years with majority of the patients 49 (35.4%) were between 51 to 60 years of age. These findings were very much comparable with Azam Z et al¹³ who had a mean age of 47 & 45 years respectively but much higher than Shaikh WM et al¹⁴ who had a mean age of 41 years. Out of the 139 patients, 88 (63.3%) were male and 51 (36.7%) were females with ratio of 1.7:1 in our study. This male predominance was also found in previous studies.¹⁴

Terlipressin improves renal function and induces natriuresis but decreases excretion of solute-free water, which can explain the development of hyponatraemia.⁷ In our study, Terlipressin induced Hyponatremia was found in 56(40.3%) patients, whereas there was no hyponatremia in 83 (59.7%) patients. Sola et al⁸ in his study showed decrease in serum sodium from 134.9±6.6 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 (5-10mEq/L) and 36% experiencing a marked decrease in serum sodium (>10mEq/L). Only 19 patients were determined to have no change in

serum sodium levels. Dunwoodie E et al¹⁵ in 2007 reported a case of 46-year-old woman who was treated with Terlipressin for bleeding esophageal varices, developed a tonic-clonic seizure and when investigated she was found to have severe hyponatremia (serum sodium=115 mmol/L). Bruha R et al¹⁶ in 2009 conducted a study on 25 patients of bleeding esophageal varices in which 15 were treated with 1 mg terlipressin every 4 hours for 5 days and 10 patients for 10 days. Serum sodium levels decreased in both groups, but returned to normal after discontinuation of terlipressin treatment.

Krag A et al¹⁷ reported that among 62 patients with bleeding esophageal varices who were treated with high-dose short-term terlipressin of 2 mg/4 h at mean 1.7 days (range 1 - 6 days) serum sodium levels decreased from 136 ± 6 to 130 ± 7 .

CONCLUSION

This study concluded that frequency of terlipressin induced hyponatremia in patients with acute variceal bleeding is very high (40.3%). So, we recommend that great care could be taken in these particular patients and regular monitoring of serum sodium levels should be done during terlipressin therapy.

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