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COMPARISON OF THE EFFICACY OF CONTINUOUS TERLIPRESSIN INFUSION VERSUS INTERMITTENT BOLUS ADMINISTRATION IN PATIENTS WITH ACUTE VARICEAL BLEEDING DUE TO PORTAL HYPERTENSION

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Abstract:

Background: Acute upper gastrointestinal bleed (AUGIB) is one of the most common medical emergencies in the UK, with an estimated incidence of 134 per 100,000, roughly equating to one presentation every 6 min [1]. Despite advances in therapeutics and endoscopy provision, mortality following AUGIB over the last two decades has remained high, with over 9,000 deaths annually in the UK [2]. Patients with suspected variceal haemorrhage should be considered for prompt administration of variceal hemorrhage measures, terlipressin (or an alternative) and antibiotics.3 Terlipressin (triglycyl-lysine vasopressin), a long-acting synthetic analogue of arginine vasopressin, has been used in the treatment of variceal bleeding in patients with end-stage liver disease and paracentesis-induced circulatory dysfunction with tense ascites as well as hepatorenal syndrome. The purpose of this study is to compare the efficacy (in preventing re-bleeding) of continuous terlipressin infusion versus intermittent bolus administration in patients with acute variceal bleeding due to portal hypertension. As routinely intermittent terlipressin bolus administration in acute variceal bleeding is used in our setups, so my study will be a useful addition in this regard as we are evaluating the efficacy of continuous infusion as compared to intermittent bolus administration for preventing re-bleeding. Then on the basis of these results, some practical recommendations can be made in our routine practice guidelines to reducing re-bleeding in these particular patients.

***Materials & Methods:** The study was conducted at the Department of Gastroenterology, Holy Family Hospital, Rawalpindi from 28th June 2022 to 27th March 2023. It was a Randomized controlled trial. A total of 106 patients with acute variceal bleeding due to portal hypertension of age 18-70 years of either gender were included. Patients with HCC, renal failure (assessed on history and s/creatinine >1.5 mg/dl), hypersensitivity to terlipressin, acid peptic disease (assessed on history) and with upper GIT bleed with sources other than esophageal varices confirmed on endoscopy were excluded. Group A received 1 mg intravenous bolus of terlipressin followed by a continuous infusion of 4 mg in 24 h. Group B received 2 mg intravenous bolus of terlipressin followed by 1 mg intravenous injection every 6 h. In both groups, all patients were undergone endoscopy and band ligation within 24 hours of admission. History of re-bleed was taken. **Results:** The mean age of patients in group A was 53.30 ± 10.45 years and in group B was 55.70 ± 10.19 years. Majority of the patients 87 (82.08%) were between 46 to 70 years of age. Out of these 106 patients, 57 (53.77%) were males and 49 (46.23%) were females with male to female ratio of 1.1:1. Efficacy in terms of no re-bleeding within one month was 47 (88.68%) in group A (continuous terlipressin infusion) and 33 (62.26%) in group B (intermittent terlipressin bolus administration) with p-value of 0.002.*

***Conclusion:** This study concluded that efficacy of continuous terlipressin infusion is better in patients with acute variceal bleeding due to portal hypertension as compared to intermittent bolus administration.*

***Keywords**: upper gastrointestinal bleeding, continuous terlipressin infusion, portal hypertension.*

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INTRODUCTION:

Acute upper gastrointestinal bleeding is defined as bleeding from a source proximal to the ligament of treitz. It is a common medical emergency and remains a major cause of morbidity and mortality. Upper gastrointestinal bleeding (UGIB) remains to be the commonest cause of critical care hospital admissions, accounting for 6-13% mortality [1]. The incidence of UGIB is 2-fold greater in males than in females, in every age group, although the death rate is comparable in the both genders [2].

Commonly it presents with hematemesis (40% to 50%) and melena (70% to 80%) while hematochezia (which mostly has colonic origin) can be present with fresh blood loss of up to 1000 ml which accounts for up to 10% of cases [3]. Although upper gastrointestinal bleeding is self-limiting in majority of the cases yet every patient with upper gastrointestinal bleeding must be properly evaluated and undergo endoscopy for diagnostic purposes as well as therapeutic endoscopy if needed.

There are multiple causes of upper gastrointestinal bleeding including portal hypertension, peptic ulcers, Mallory weiss tear, vascular anomaliesve gastritis. Peptic ulcers remain one of the leading cause of upper gastrointestinal bleeding in West accounting up to 40% while portal hypertension being second leading cause with 10-20% incidence [4]. While according to a study conducted in Egypt variceal causes of bleeding were the most common representing 70.1% followed by non-variceal causes 26.1% and obscure causes 3.8% [6]. According to various other studies the 1 year rate of variceal bleeding is 12%. Frequently it is caused by gastro-duodenal ulcers (gastric ulcers in 24.4% and duodenal ulcers 20.6%, portal gastropathy in 14.4%, Mallory Weiss tear in 11.3% and gastro-duodenal erosions in 10.6% [6].

Acute upper gastrointestinal bleed (AUGIB) is one of the most common medical emergencies in the UK, with an estimated incidence of 134 per 100,000, roughly equating to one presentation every 6 min [7]. Despite advances in therapeutics and endoscopy provision, mortality following AUGIB over the last two decades has remained high, with over 9,000 deaths annually in the UK [8] [9].Patients with suspected variceal hemorrhage should be considered for prompt administration of variceal measures, terlipressin (or an alternative) and antibiotics.

Terlipressin (triglycyl-lysine vasopressin), a long-acting synthetic analogue of arginine vasopressin, has been used in the treatment of paracentesis-induced circulatory dysfunction with tense ascites as well as hepatorenal syndrome and variceal bleeding in patients with end-stage liver disease [10]. It is a vasopressin analogue, increases systemic vascular resistance, reduces cardiac output, and reduces portal pressures by approximately 20% [11].

Although there have been relatively few studies of plasma concentrations after bolus injection, bolus injection of 0.5 – 1.0 mg terlipressin is clinically preferred because of the long-lasting effect of the drug [12]. It has been suggested that bolus injection may cause sustained global or regional vasoconstriction [13].A study has shown that continuous infusion of terlipressin may be more effective than intermittent infusion to prevent treatment failure in patients with variceal bleeding [14]. Jha SK et al has shown re-bleeding in 4.7% patients with continuous terlipressin infusion and 20.7% in patients with intermittent terlipressin bolus administration [14].

As routinely intermittent terlipressin bolus administration in acute variceal bleeding is used in our setups, so our study will be a useful addition in this regard as we are evaluating the efficacy of continuous infusion as compared to intermittent bolus administration for preventing re-bleeding. Then on the basis of these results, some practical recommendations can be made in our routine practice to reduce re-bleeding in these particular patients.

MATERIALS AND METHODS:

STUDY DESIGN:

Randomized controlled trial.

SETTING:

Department of Gastroenterology, Holy Family Hospital, Rawalpindi.

DURATION OF STUDY:

28th June 2022 to 27th March 2023.

SAMPLE SIZE:

Sample size of 106 (53 in each group) cases has been calculated with 95% confidence level, 80% power of study and taking re-bleeding in 4.7% patients with continuous terlipressin infusion and in 20.7% patients with intermittent terlipressin infusion.

SAMPLE TECHNIQUE:

Non-probability, consecutive sampling followed by random allocation in both groups.

SAMPLE SELECTION:

a. Inclusion Criteria:

- All patients with acute variceal bleeding due to portal hypertension (as per-operational definition.
- Age 18-70 years of wither gender.

b. Exclusion Criteria:

- Patients with hepatocellular carcinoma.
- Patients with renal failure (assessed on history and s/creatinine >1.5 mg/dl).
- Patients with hypersensitivity to terlipressin.
- Patients with acid peptic disease (assessed on history).
- Patients with upper GIT bleed with sources other than esophageal varices confirmed on endoscopy

DATA COLLECTION PROCEDURE:

After approval from the ethical review committee, total number of 106 patients admitted to the department of Gastroenterology, Holy Family Hospital, Rawalpindi, fulfilling the inclusion criteria was selected. After taking informed written consent, the selected patients were placed randomly into two equal groups i.e. Group A (study group, continuous terlipressin) & Group B (reference group, intermittent, terlipressin method) by computer generated random number list. Then, after all initial resuscitative measures, terlipressin therapy was started in each patient. Group A received 1 mg intravenous bolus of terlipressin followed by a continuous infusion of 4 mg in 24 h. Group B received 2 mg intravenous bolus of terlipressin followed by 1 mg intravenous injection every 6 h. In both groups, all patients were undergone endoscopy and band ligation within 24 hours of admission. Patients were managed as per standard operating procedures in the department. Patients were discharged after being stable and were followed up weekly for one month. On each follow up patients were examined for routine examination. Necessary investigations were done. History of re-bleed was taken. The researcher personally got relevant data if patients presented in the same hospital for re -bleed and hospital record was taken for patients who presented in emergency department of any other health facility. The maximum duration of follow up for the study was one month. And data was collected for re-bleed as per operational definition. This all data (age, gender, severity of disease as per child-Pugh score, grades of esophageal varices) was noted on a pre-designed proforma (Annexure I).

DATA ANALYSIS PROCEDURE:

Collected data was analyzed through computer software SPSS 25.0. Mean and standard deviation were calculated for quantitative variable; age. Frequency and percentage were calculated for qualitative variables like gender, child pugh class, variceal grade and efficacy. The two groups were compared for the outcome variable i.e. efficacy using chai square test or fisher exact test.

Effect modifiers like age, gender and disease severity as per child- Pugh score and grades of varices were controlled through stratification and post-stratification chi square or fisher exact test be used. 95% confidence level, P-value ≤0.05 was considered as significant for all statistical tests in the study.

RESULTS:

Age range in this study was from 18 to 70 years with mean age of 54.33 ± 10.31 years. The mean age of patients in group A was 53.30 ± 10.45 years and in group B was 55.70 ± 10.19 years. Majority of the patients 87 (82.08%) were between 46 to 70 years of age as shown in Table II.

Out of these 106 patients, 57 (53.77%) were males and 49 (46.23%) were females with male to female ratio of 1.1:1 (Table II). Distribution of patients according to child pugh class and grades of varices is shown in Table III & IV respectively.

Efficacy in terms of no re-bleeding within one month was 47 (88.68%) in group A (continuous terlipressin infusion) and 33 (62.26%) in group B (intermittent

terlipressin bolus administration) with p-value of 0.002 as shown in Table V.

Stratification of efficacy of both groups according to age groups and gender is shown in Table VI & VII respectively while Table VIII & IX have shown the stratification of efficacy with respect to child pugh class and grades of varices.

Table-I: Age distribution for both groups.

	Group A (n=53)		**Group B (n=53)**		**Total (n=106)**	
Age (years)	No. of patients	%age	No. of patients	%age	No. of patients	%age
18-45	11	20.75	08	15.09	19	17.92
46-70	42	79.25	45	84.91	87	82.08
Mean ± SD	**53.30 ± 10.45**		**55.70 ± 10.19**		**54.33 ± 10.31**	

Table-II: Distribution of patients according to gender.

Gender	**Group A (n=53)**		**Group B (n=53)**		**Total (n=106)**	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
Male	28	52.83	29	54.72	57	53.77
Female	25	47.17	24	45.28	49	46.23

Table III: Distribution of patients according to child pugh class

Class	**Group A (n=53)**		**Group B (n=53)**		**Total (n=106)**	
	Frequency	%age	Frequency	%age	Frequency	%age
A	15	28.30	18	33.96	33	31.13
B	24	45.28	20	37.74	44	41.51
C	14	26.42	15	28.30	29	27.36

Table IV: Distribution of patients according to grades of varices

Grades	**Group A (n=53)**		**Group B (n=53)**		**Total (n=106)**	
	Frequency	%age	Frequency	%age	Frequency	%age
I	10	18.87	08	15.09	18	16.98
II	34	64.15	36	67.92	70	66.04
III	09	16.98	09	16.98	18	16.98

Table V: Comparison of Efficacy between both Groups (n=106).

		Group A (n=53)		**Group B (n=53)**	
		No. of Patients	%age	No. of Patients	%age
EFFICACY	**Yes**	47	88.68	33	62.26
	No	06	11.32	20	37.74

- **P value is 0.002 which is statistically significant**.

Table VI: Stratification of efficacy of both groups according to age groups.

Age of patients	Group A (n=53)		Group B (n=53)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
18-45 years	11	00	06	02	**0.080**
46-70 years	36	06	27	18	**0.007**

Table VII: Stratification of efficacy of both groups according to gender.

Gender	Group A (n=53)		Group B (n=53)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
Male	25	03	18	11	**0.017**
Female	22	03	15	09	**0.038**

Table VIII: Stratification of efficacy of both groups according to child pugh class.

Class	Group A (n=53)		Group B (n=53)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
A	14	01	12	06	**0.062**
B	20	04	13	07	**0.162**
C	13	01	08	07	**0.017**

Table IX: Stratification of efficacy of both groups according to grades of varices.

Grades	Group A (n=53)		Group B (n=53)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
I	08	02	04	04	**0.180**
II	31	03	26	10	**0.042**
III	08	01	03	06	**0.016**

DISCUSSION:

Cirrhosis and portal vein thrombosis are two of the primary causes of severe portal hypertension—an increase in blood pressure of the (portal) vein between digestive organs and the liver. This increase in pressure contributes to the development of varices, or large veins, that can weaken over time and lead to gastrointestinal bleeding. Terlipressin is commonly used to treat acute variceal bleeding. It is a synthetic vasopressin analogue with fewer side-effects and a longer half-life than vasopressin, is effective in controlling acute variceal bleeding [15]. 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 [15]. In acute variceal bleeding, terlipressin may have an added advantage as it can potentially reverse hepatorenal syndrome. In addition, it has been shown to have a more sustained haemodynamic effect compared to treatment with octreotide [16].

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 [17]. Terlipressin is as effective as any other effective therapy, including endoscopic injection sclerotherapy, and is safer than vasopressin + nitroglycerin and endoscopic injection

sclerotherapy [17][18]. The overall efficacy of terlipressin in controlling acute variceal bleeding at 48 hours is 75 to 80% across trials[92] and 67% at 5 days [18]. Terlipressin is also useful in hepatorenal syndrome. Thus the use of terlipressin for variceal bleeding may prevent renal failure, which is frequently precipitated by variceal bleeding. 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 patients [18] and reverse after drug withdrawal.

We have conducted this study to compare the efficacy (in preventing re-bleeding) of continuous terlipressin infusion versus intermittent infusion in patients with acute variceal bleeding due to portal hypertension. Age range in this study was from 18 to 70 years with mean age of 54.33 ± 10.31 years. The mean age of patients in group A was 53.30 ± 10.45 years and in group B was 55.70 ± 10.19 years. Majority of the patients 87 (82.08%) were between 46 to 70 years of age. Out of these 106 patients, 57 (53.77%) were males and 49 (46.23%) were females with male to female ratio of 1.1:1. Efficacy in terms of no re-bleeding within one month was 47 (88.68%) in group A (continuous terlipressin infusion) and 33 (62.26%) in group B (intermittent terlipressin infusion) with p-value of 0.002. Jha SK et al has shown re-bleeding in 4.7% patients with continuous terlipressin infusion and 20.7% in patients with intermittent terlipressin infusion [14].

Terlipressin, a synthetic analogue of vasopressin that has a longer biological activity and significantly fewer side effects, i.e. effective in controlling acute variceal hemorrhage and has been associated with a decrease mortality [19]. Terlipressin is given as a 2g bolus dose every 4 hours during the first 2 d. The dose is halved after bleeding is controlled and can be maintained for up to 5 days. Administration of terlipressin at low doses in continuous perfusion has been tested in cirrhotic patients with septic shock with promising results [20][21].

CONCLUSION:

This study concluded that efficacy (in preventing rebleeding) of continuous terlipressin infusion is better in patients with acute variceal bleeding due to portal hypertension as compared to intermittent bolus administration. So, we recommend that continuous terlipressin infusion should be preferred in patients with acute variceal bleeding due to portal hypertension for saving these patients life.

REFERENCES:

1. Alatise OI, Aderibigbe AS, Adisa AO, Adekanle O, Agbakwuru AE, Arigbabu AO. Management of overt upper gastrointestinal bleeding in a low resource setting: a real world report from Nigeria. BMC Gastroenterol. 2014;14(1):210.
2. Dewan KR, Patowary BS, Bhattarai S. A study of clinical and endoscopic profile of acute upper gastrointestinal bleeding. Kathmandu Uni Med J. 2015;12(1):21-5.
3. Papadakis MA, Mcphee SJ. Current Medical Diagnosis and treatment 55th Edition, McGrawhill Education; 2016;584-7.
4. McQuaid KR. Gastrointestinal disorders. In: Papadakis MA,McPhee SJ, Rabow MW, editors. Current medical diagnosis and treatment. 52nd Ed. New York: McGraw-Hill; 2013:564-661.
5. Elwakil R, Reda MA, Abdelhakam SM, Ghoraba DM, Ibrahim WA. Causes and outcome of upper gastrointestinal bleeding in emergency endoscopy unit of Ain Shams University Hospital. J Egypt Soc Parasitol. 2011;41:455-67.
6. Hadayat R, Jehangiri A, Gul R, Khan AN, Said K, Gandapur A. Endoscopic findings of upper gastrointestinal bleeding in patients with liver cirrhosis. J Ayub Med Coll Abbottabad. 2015;27(2):391–4.
7. National Confidential Enquiry into Patient Outcome and Death (NCEPOD). Time to get control? A review of the care received by patients who had a severe gastrointestinal haemorrhage. 2015. http://www.ncepod.org.uk/2015report1/downloads/TimeToGetControlFullReport.pdf.
8. Siau K, Chapman W, Sharma N, Tripathi D, Iqbal D, Bhala N. Management of acute upper gastrointestinal bleeding: an update for the general physicians. J R Coll Physicians Edinb. 2017;47:218–30.
9. Gralnek I, Dumonceau J, Kuipers E. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2015;47: 1–46.
10. Xinmiao Z, Dhiraj T, Tingxue S, Lichun S, Bing H, Jia Z, et al. Terlipressin for the treatment of acute variceal bleeding: a systematic review and meta-analysis of randomized controlled trials. Medicine. 2018;97(48):e13437.
11. Cavallin M, Piano S, Romano A, Fasolato S, Frigo AC, Benetti G, et al. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: a randomized controlled study. Hepatol. 2016;63:983-92.

12. Cavallin M, Kamath PS, Merli M, Fasolato S, Toniutto P, Salerno F, et al. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: a randomized trial. Hepatol. 2015;62:567-74.
13. Papaluca T, Gow P. Terlipressin - current and emerging indications in chronic liver disease. J Gastroenterol Hepatol 2018;33:591–8.
14. Jha SK, Mishra M, Jha A, Dayal VM. Comparison of continuous versus intermittent infusions of terlipressin for the control of acute variceal bleeding in patients with portal hypertension: An open-label randomized controlled trial. Indian J Gastroenterol. 2018;37(4):313-20.
15. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. Cochrane Database Syst Rev. 2003;(1):CD002147
16. Fallah MA, Prakash C, Edmundowicz S. Acute gastrointestinal bleeding. Med Clin North Am. 2000 Sep. 84(5):1183-208.
17. Bolognesi M, Balducci G, Garcia-Tsao G, Gatta A, Gines P, Merli M, et al. Complications in the medical treatment of portal hypertension. Portal Hypertension III. Proceedings of the Third Baveno International Consensus Workshop on Definitions, Methodology and therapeutic Strategies.Oxford,UK:Blackwell Science, 2001:180-203.
18. D'Amico G, Pagliaro L, Bosch J, Pharmacological treatment of portal hypertension: an evidence based approach. Semin Liver Dis 1999;19:475-505.
19. Morelli A, Ertmer C, Lange M, Westphal M. Continuous terlipressin infusion in patients with septic shock: less may be best, and the earlier the better? Intensive Care Med 2007;33:1669-1670.
20. D'Amico G, Pagliaro L, Bosch J, Pharmacological treatment of portal hypertension: an evidence based approach. Semin Liver Dis 1999;19:475-505.
21. Morelli A, Ertmer C, Lange M, Westphal M. Continuous terlipressin infusion in patients with septic shock: less may be best, and the earlier the better? Intensive Care Med 2007;33:1669-1670.