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COMPARISON OF TERLIPRESSIN AND OCTREOTIDE IN INITIAL MANAGEMENT OF ACUTE VARICEAL BLEEDING.

1. **IMDAD ALI ANSARI**
FCPS
2. **AZIZULLAH JALBANI**
MCPS, FCPS
3. **AFTAB HUSSAIN SHAH**
FCPS
4. **KOURO MAL GURBAKHSHANI**
FCPS
5. **GHULAM AKBAR SOLANGI**
FCPS
6. **ABRAR SHAIKH**
MRCP, FRCP

1. ***Assistant Professor***
MEDICINE, CHANDKA MEDICAL COLLEGE, ARKANA.
2. ***Assistant Professor***
MEDICINE, CHANDKA MEDICAL COLLEGE, ARKANA.
3. ***Associate Professor***
MEDICINE, CHANDKA MEDICAL COLLEGE, ARKANA.
4. ***Assistant Professor***
MEDICINE, CHANDKA MEDICAL COLLEGE, ARKANA.
5. ***Professor***
MEDICINE, CHANDKA MEDICAL COLLEGE, ARKANA.
6. ***Professor, Dean Faculty of Medicine***
SHAHEED MUHTARMA BENAZEER BHUTTO MEDICAL UNIVERSITY, LARKANA, SINDH.

Correspondence:
DR. AZIZULLAH JALBANI
CELL NO0300 - 3410730
Phone No. 074-4041234
E-MAILazizjalbani@yahoo.com

ABSTRACT

Most patients due to cirrhosis develop esophageal varices due to portal hypertension and present with acute and often fatal gastrointestinal (G.I) bleeding. The purpose of this study was to establish Octreotide or Terlipressin, as the first line of pharmacological therapies in controlling acute variceal bleeding, particularly where the facilities for ligation and banding are not available

OBJECTIVES:*To compare the efficacy of Terlipressin and Octreotide in initial management of acute variceal bleeding.To document the safety of Terlipressin and Octreotide in initial management of acute variceal bleeding.*

STUDY DESIGN:*Single blinded, comparative study.*

SETTING:*Medical-II wards, Chandka Medical Collage Hospital (CMCH) Larkana.*

DURATION WITH DATES:*One year from March 2007 to March 2008.*

SUBJECTS AND METHODS:*57 patients, who reported with acute upper G.I bleeding, were included and divided alternatively in two groups. Group A (22) patients were given injection Terlipressin where as Group B (35) patients received injection Octreotide. Treatment was continued at least for 03 days in both groups.*

RESULTS:*Bleeding was controlled in 21 (95.4%) patients of Group A and 26 (74.2%) patients of Group B (P=0.392). Re-bleeding was seen in 01 (2.85%) patient of Group B. Failure of therapy was noted in 09 (25.71%) patients of Group B (P=0.063). Mortality was also higher in Group B (28.5%) (P=0.04). Both therapies had no side effects.*

CONCLUSION:*Both vasoactive agents were effective and safe but Terlipressin had slight edge over Octreotide due to its simple intravenous dosage and rapid haemostasis.*

KEY WORDS: Octreotide, Terlipressin, Variceal bleeding, Endoscopic Ligation, Endoscopic Banding, Upper G.I bleeding, Vasoactive agents, Haemostasis.

INTRODUCTION

The Hepatitis B virus (HBV) carriers are approximately 4.5 millions,[1] whereas approximately 10 millions of people are infected with Hepatitis C virus (HCV), [2] in Pakistan. Unlike many chronic diseases, advanced liver disease evolves into a host of secondary metabolic and circulatory disorders that eventually divert the focus of treatment from the primary organ disease to its complications.

Most patients with cirrhosis develop esophageal varices due to portal hypertension, at some time during their disease. They have 25–35% risk of developing initial variceal bleeding, especially during the first year after varices have been diagnosed and mortality with it is 24–35%. [3] Survivors of an initial bleed have even higher risk of re–bleed up to 30–50%, [4] usually with in 06 months. Risk of death up to 30–50% [5] from each episode, making it one of the commonest medical emergencies in our country. The bleeding stops on its own in 70% of patients before they reach the hospital, however early re–bleeding occurs within hours or days in at least 50% of cases. The risk of continued variceal bleeding or early re–bleeding within first 06 hours is related to severity of liver disease. [5,6,7] Factors that incite bleeding and re–bleeding, are not fully understood [8], however bleeding does not occur until the hepatic venous pressure exceeds 12 mmHg. [9,10] The variceal bleeding may also complicate or precipitate hepatic encephalopathy, hepatorenal syndrome, necessitating its early treatment, specially in intensive care unit of a hospital. Octreotide, a somatostatin derivative is as effective as vasopressin in acute variceal bleeding, [11,12] used in infusion form. Recent studies show that terlipressin, a synthetic analogue of

TABLE NO: - I
AGE & SEX DISTRIBUTION
N = 57

	Group A n = 22			Group B n = 35		
Age in years	**Male**	**Female**	**Total patients %**	**Male**	**Female**	**Total patients %**
18 – 30	02	04	6 (27.2%)	09	03	12 (34.2%)
31 – 40	03	04	7 (31.8%)	06	——-	6 (17.1%)
41 – 50	05	02	7 (31.8%)	08	02	10 (28.5%)
51 – 60	01	01	2 (9%)	06	01	7 (20%)

KEYS: -
Group A = Terlipressin treated group (22) of patients.
Group B= Octreotide treated group (35) of patients.

vasopressin, effectively controls variceal bleeding with a lowrate of side effects, [13] even when used for extended period. Furthermore it has the advantage of simple intravenous bolus regimen.

OBJECTIVES

The objectives of this study were:
i) To compare the efficacy of Terlipressin and Octreotide in initial management of acute variceal bleeding.
ii) To document the safety of Terlipressin and Octreotide in initial management of acute variceal bleeding.

METHODOLOGY

1. SETTING**:**Wards of Medical Unit – II, CMCH Larkana.
2. DURATION OF STUDY

One year (March 2007 to March 2008).

3. SAMPLE SIZE

57 patients were included in this study.

4. SAMPLING SELECTION

During the period of March 2007 to March 2008, adult patients of either sex, who reported to the casualty of CMCH Larkana.

Inclusion Criteria

All patients of upper G.I bleeding admitted in Medical Unit-II, CMCH Larkana, with following criteria, were included in this study.
18 – 60 years of age.
Esophago–gastro–duodenoscopy (EGD scopy) revealed varices as a sole cause of their upper G.I bleeding.
No bleeding ulcer on EGD scopy.
Presence of signs of chronic liver disease, like: palmer erythema, pallor, jaundice, spider angioma, gynaecomastia, pedal edema, shrunken liver, enlarged spleen and ascites.
Presence of ultrasonographic findings, suggestive of chronic liver disease with portal hypertension, eg: shrunken liver, splenomegaly, ascites and dilated portal vein.

Exclusion Criteria

Known cases of hypertension or had high blood pressure, at the time of admission.
Known cases of renal failure.
Patients with ischemic heart disease.
Ulcer on EGD scopy.
Age above 60 years.
Upper G.I endoscopy revealed malignancy.

5. STUDY DESIGN

Single blinded, Comparative study.

DATA COLLECTION

Adult patients of either sex, who reported to the casualty of CMCH Larkana with upper G.I bleeding in the last 24 hours, were admitted in the wards of Medical Unit-II. All these patients were briefly informed about this study and a written consent was obtained from them (and attendants of unconscious patients) before enrollment. These patients were divided alternatively in two groups i.e Group A & Group B and every thing was written on a proforma, specially prepared for this study. Detailed history of these patients was taken with special reference to the symptoms of chronic liver disease. A detailed past medical and family history, was recorded to find out any etiological factor of their liver disease such as alcohol, drugs history, blood transfusions, needle pricks, operations and contact with jaundiced patients. Detailed physical examination was done in all patients, with special reference to the presence of peripheral signs of chronic liver disease, like pallor, jaundice, pedal edema, clubbing, palmer erythema, spider angioma, loss of pubic and axillary hairs, gynaecomastia and testicular atrophy in male patients and breast atrophy in female patients. Abdominal examination was done in detail specially to find out enlarged spleen, size of liver and ascites. All the routine and relevant investigations were sent to a single laboratory i.e Centeral Laboratory, CMCH Larkana, assigned for this study. Upper G.I endoscopy was performed within 24 hours.
Group A patients received injection Terlipressin as first line of therapy, in the dose of 2mg I/V x stat and then 1mg I/V x 6 hourly.
Group B patients were given 50 microgram bolus of injection Octreotide, followed by 50 microgram/hour as intravenous therapy in burette/ chamber, diluted with normal saline to make a total amount of 100 ml, for 48 hours and thereafter 50 micrograms subcutaneously x 06 hourly. for 75 hours. Other therapy like blood transfusions and intravenous fluids, were given according to the patient's requirements. Vitamin k and proton pump inhibitors were used in all patients, in the doses of 10mg I/V daily and 40mg I/V daily, respectively. Medical treatment was continued at least for 03 days, whether bleeding stopped or not. Treatment was considered unsuccessful, when fresh bleeding from mouth and or rectum continued, despite 03 days medical treatment.
The primary outcome measure was mortality. Secondary outcomes were failure of haemostasis upto 03 days, re-bleeding within first 03 days, adverse effects of drugs, transfusion requirements and length of hospitalization.

STATISTICAL ANALYSIS

Statistical packages for social science (SPSS 7.0) was used to analyze data. Chi-Squire test was also applied to check the proportion difference between

TABLE NO: -II
SIGNS OF GROUP A & GROUP B PATIENTS AT ADMISSIOIN
N = 57

Signs	Group A (Terlipressin) N = 22		Group B (Octreotide) N = 35	
	No. of Patients	Percentage	No. of Patients	Percentage
Fever	07	31.8%	09	25.7%
Anemia	22	100%	35	100%
Jaundice	20	90.9%	29	82.8%
Pedal edema	17	77.2%	27	77.1%
Palmer erythema	05	22.7%	12	34.2%
Leuconychia	13	59%	26	74.2%
Koilonychia	05	22.7%	03	8.5%
Clubbing	04	18.1%	11	31.4%
Asterixis	10	45.4%	11	31.4%
Spider angioma	02	09%	03	8.5%
Cyanosis	00	00%	01	2.8%
Scratch marks	00	00%	01	2.8%
Fetar hepaticus	04	18.1%	11	31.4%
Wasting	02	09%	09	25.7%
Increased pigmentation	02	09%	05	14.2%
Gynaecomastia	02	09%	08	22.8%
Testicular atrophy	02	09%	05	14.2%
Ascites	19	86.3%	31	88.5%
Reduced liver span	10	45.4%	18	51.4%
Enlarged spleen	22	100%	34	97.1%
Encephalopathy	13	59%	25	71.4%
Signs	**Mean ±SD**		**Mean ±SD**	
Pulse / minute	92 ± 15		92 ± 15	
Mean Systolic B.P (mmHg)	93.18 ± 35		89.28 ± 29	
Mean Diastolic B.P (mmHg)	56.81 ± 8		54.57 ± 10	

KEYS: -Systolic B.P = Systolic Blood Pressure.
Diastolic B.P = Diastolic Blood Pressure.

Terlipressin (Group A) and Octreotide (Group B) for the control of bleeding, failure of therapy and mortality with 0.05 level of significance.

RESULTS

Included 57 patients with upper G.I bleeding. Including 40 (70.1%) males & 17 (29.8%) female patients, divided into 04 age groups. Majority of these patients were in the range of 41 to 50 years. (Table No. I) Pallor was seen in all patients of both groups, followed by splenomegaly, observed in 22 (100%) and 34 (97.1%) patients in Group A & Group B, respectively. (Table No. II) Results of investigations showed that esophageal varices were complicated by the presence of spontaneous bacterial peritonitis (SBP) in 03 (8.5%) patients of Group B. Investigations showed that 10 (45.4%) patients belonged to Group A, had HCV, the cause of their chronic liver disease. On the other hand, HBV was the etiological factor in 14 (40%) patients, who belonged to Group B. Both HBsAg and Anti HCV were present in 2 (9%) patients of Group A and 06 (17.1%) patients of Group B. Result of Biochemical examination is shown in (Table No. III)

In Group A, 02 (9%) patients had grade-I varices, 10 (45.4%) patients had grade-II varices, whereas 10 (45.4%) patients showed grade-III esophageal varices.

In Group B, 02 (5.7%) patients had grade-I varices, 16 (45.7%) patients were found to have grade-II varices, whereas 17 (48.5%) patients had grade-III esophageal varices. In Group A (22) patients, treated with Terlipressin, acute variceal bleeding was controlled in 21 (95.4%) patients. Whereas, in Group B (35) patients, treated with Octreotide, successful haemostasis was achieved in 26 (74.2%) patients. There is no statistical significant difference (P=0.392) between Group A & Group B patients in this aspect of result.

Among 21 (95.4%) patients of Group A, who showed successful control of acute variceal bleeding, 10 (47.61%) patients showed control of bleeding within first 18 hours of therapy in comparison to 06 (23.07%) patients of Group B (P=0.05). 07 (33.33%) patients of Group A, showed haemostasis up to 24 hours in comparison to 09 (34.61%) patients of Group B (P=0.672). In Group A, 04 (19%) patients out of 21 (95.4%) patients, were found bleeding free up to 03 days of therapy in comparison to 11 (42.3%) patients, out of 26 (74.2%) patients of Group B (P=0.343). In Group A patients, Terlipressin failed to control acute variceal bleeding in 01 (4.5%)

TABLE NO:III
BIOCHEMICAL MEAN VALUES OF GROUP A & GROUP B PATIENTS AT THE TIME OF ADMISSION
N=57

Biochemical Parameter	Group A (N=22) Mean # SD	GroupB (N=35) Mean # SD
Hemoglobin (gm/dl)	8.72#2.76	8.41# 1.9
Plateletes (mm^3)	103206#45316	100103#41218
Blood Urea (mg/dl)	49.9#12.1	53.05# 18.2
Serum Creatinine (mg/dl)	01#1.22	1.54 # 1.13
Bilirubin (mg/dl)	3.12#6.18	3.24 # 3.55
ALT(IU/L)	88.54 # 71.8	94.45 # 72.52
PT (seconds)	4.14#7.15	4.34 #4.11
S.Proteins (gm/dl)	4.8 # 1.53	4.44# 1.12
Ascitic Fliid Protein (gm/dl)	02 # 0.88	1.84 # 0.92
Ascitic Fliid Neutrophils ($cell/mm^3$)	08 #5.2	101# 82.1

Keys:
P.t=Prothrombin Time
ALT=Alanine Aminotransferase.
Group A=Terlipressin treated group (22) og patients.
Group B= Octreotide treated group (35) of Patients.

TABLE NO: IV
COMPARISON OF TERLIPRESSIN AND OCTREOTIDE TREATMENT OUTCOME IN PATIENTS OF GROUP A & GROUP B
N=57

S.NO:	PARAMETER	GROUP A (Terlipressin) N=22	GROUP B (Octreotide) N=35	P= VALUE
01	Control of bleeding	21 (95.4%)	26 (74.2%)	0.392
i	Haemostasis within 1st 18 hours of therapy	10(47.61%)	06 (23.07%)	0.05*
ii	Haemostasis within 1st 24 hours of therapy	07 (33.33%)	09 (34.61%)	0.672
iii	Haemostasis up to 03 days of therapy	04 (19%)	11 (42.3%)	0.343
02	Failure of therapy	01 (4.5%)	09 (25.71%)	0.063
03	Re-bleeding	00%	01(2.85%)	
04	Mortality	01 (4.5%) 10	(28.5%)	0.04*

NOTE: Adverse effects of both therapies were not observed.
*Significant Chi-Square test.

patient compared with 09 (25.71%) patients of Group B, treated with Octreotide (P= 0.063).

Re-bleeding was observed in 01 (2.85%) patient of Octreotide treated Group B.In Group A patients, who were treated with Terlipressin, 01 (4.5%) patient expired in comparison to 10 (28.5%) patients of Group B, who were given Octreotide (P= 0.04). In Group A, 01 (4.5%) patient, who expired (after 06 days hospital stay), was suffering from advance liver disease with Child Pugh's Class-C.Among 10 (28.5%) patients, who expired in Group B, 02 (20%) patients expired within 03 days of hospital stay and 08 (80%) patients had hospital stay up to or more than 05 days. Out of these 10 (28.5%) expired patients in Group B, 01 (2.85%) patient, who showed control of variceal bleeding initially, expired due to re-bleeding. Whereas in rest of the other 09 (25.71%) expired patients, the drug remained unsuccessful to control acute variceal bleeding. All these 10 (28.5%) expired patients were suffering from advanced liver disease with Child Pugh's Class-C. Hyperglycemia was observed in 01 known diabetic patient of Group B, after the bolus dose of Octreotide (may be related to oral sweets or missed dose of oral hypoglycemic drug).

The average blood transfusions required in Group A (22) patients, were 03 packs in comparison to 4.35 packs for Group B (35) patients.

The average stay of hospital in Group A (22) patients, was 8.75 days in comparison to 7.71 days for Group B (35) patients (Table No. IV).

DISCUSSION

In this study, the incidence of esophageal varices in Cirrhotic patients was 100%. This figure is higher than reported from other studies, conducted in foreign countries i.e. 80% to 90%. The reason for this higher incidence of esophageal varices in our areas may be due to the poverty so that patients do not seek medical advice at an early stage and early signs are ignored. Upper G.I endoscopy revealed grade-II varices in 45.6% of patients and grade-III varices were found in 47.36% of cases. Whereas one study of WM Shaikh et al 2000, conducted at Larkana[14], showed 84% of patients in grade-III. This may be due to the fact that most of our patients are now well aware and tend to seek medical advice on first episode of complication. This is again explained by the increased bulk of patients in grade-II, in this study.

In this study, both vasoactive drugs were well tolerated. Hyperglycemia with the bolus dose of Octreotide was noted in one known diabetic patient. It may be related to the missed dose of oral hypoglycemic drug.

01 (4.5%) patient from Group A (treated with Trelipressin) and 10 (28.5%) patients from Group B (treated with Octreotide), expired. This siginificant statistical difference (P=0.04) for mortality in Octreotide treated Group B patients in comparison to Terlipressin treated Group A patients may partly be related to the increased number (42.8%) of Child-Pugh's Class-C (P=0.912) patients in Group B in comparison to (40.9%) Terlipressin treated Group A patients. This difference may also be influenced by the presence of SBP in 8.5% of patients in Group B. Moreover, the incidence of presence of both HBsAg and Anti HCV simultaneously, was observed in 17.1% of Octreotide treated group, in comparison to 9% in Terlipressin treated Group A patients.

CONCLUSION

Results of this study conclude that both terlipressin and octreotide are safe, cost effective and readily available modes of treatment, in patients who come to you at clinic, with upper G.I bleeding, where endoscopic facilities and trained personnel are not available.

In comparing these agents, terlipressin has slight edge over octreotide. Because, terlipressin is easily administered in an emergency situation like massive variceal bleeding, via simple I/V bolus injection, unlike other agents which require continuous infusion. It rapidly induces haemostasis and is free from vasopressin like side effects. However, the major advantage of terlipressin use is that, it is the agent to have been shown to reduce mortalilty in bleeding esophageal varices.In the light of this study, it is suggested that, terlipressin should be used early in patients with suspected variceal bleeding, to reduce bleeding related mortality, even prior to admission in hospital for more definite treatment options like EVS / EVL / banding.

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