OCTREOTIDE OR CONVENTIONAL THERAPY FOR VARICEAL HAEMORRHAGE

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SUMMARY

To study whether octreotide is more effective than conventional conservative management for treating bleeding oesophageal varices, and to know whether ocreotide has any beneficial effect on survival, patients suspected of bleeding from oesophageal varices and having cirrhosis of the liver patients admitted in the Department of Medicine, Lady Reading Hospital, Peshawar were studied. Within the limited power of this study we were unable to show a clinical benefit of octreotide in the emergency treatment of bleeding oesophageal varices. Moreover, the mortality rate was recorded to be higher in the octreotide group.

INTRODUCTION

Somtostatin is a ubiquitous tetradecapeptide hormone. In most experimental studies, both in animals and in human, it has reduced portal blood flow, while the effects on intravaricael pressure has been more equivocal. Somatostatin and its derivative octreotide are often used for emergency treatment of bleeding oesophageal varices in patients with cirrhosis of liver. Three placebo controlled trails and meta analysis of the trails, however, have shown contrasting results.

To study whether octreotide is more effective than conventional conservative management for treating bleeding oesophageal varices and to know whether octreotide has any beneficial effect on survival, patients suspected of bleeding from oesophageal varices and having cirrhosis of the liver patients admitted in the Department of Medicine, Lady Reading Hospital, Peshawar were studied.

MATERIAL AND METHODS

All the patients presenting with haematemesis or melena (or both) were admitted in the medical unit from December 1996 to December 1997. Those with clinical indication of bleeding oesophageal varices and with verified or suspected cirrhosis of liver were eligible for the study. Children, pregnant and lactating women and those who had sclerotherapy done within the previous 10-15 days were not included in this study.

On entry and during their stay in the hospital we noted the duration of bleeding, episodes of rebleeding, hepatomegaly, splenomegaly, presence of encephalopathy and ascites. Serum concentration of bilirubin, aspartate transferase, albumin, total protein, haemoglobin, prothrombin time, HBS antigen and anti HCV antibody were done for all the patients.

Treatment protocol for each bleeding episode included subcutaneous injection of

TABLE – I

BASE LINE CHARACTER OF 50 PATIENTS WITH ACUTE VARICEAL BLEEDING TREATED WITH OCTREOTIDE OR CONVENTIONAL THERAPY

	OCTREOTIDE GROUP	NON OCTEROTIDE GROUP
NUMBER OF PATIENTS	30	20
AGE (Yrs) MEAN/RANGE	42 (30-70)	40 (28-60)
MALE	18	12
PORTAL HYPERTENSION AETIOLOGY		
HEPATITIS-B	10	06
HEPATITIS-C	18	11
HEPATITIS B & C	01	0
NON VIRAL CIRRHOSIS	01	03
SPLENOMEGALY	20	14
HEPATOMEGALY	06	04
MEAN HAEMOGLOBIN (g/dl)	07 (5-10)	09 (6.3-11.2)
CREATININ	01	01
DEATHS, DAYS (3-10) (NO. OF PATIENTS)	08 (27.03%)	04 (20%)
ENDOSCOPY DAYS 2-10) (NO OF PATIENTS)	09	09
OESOPHAGEAL VARICES		
GRADE-III	06	07
GRADE-II	06	05
FUNDAL VARICES		
GRADE-III	03	04
GRADE-II	06	05
GASTROPATHY	05	06
ACTIVE BLEEDING	02	03
DUODENAL ULCER	0	0
NO OF BLOOD TRANSFUSION	02 (0-15)	2.1 (0-9)
DURATION OF STAY IN HOSPITAL IN DAYS	7.5 (5-13)	08 (5-17)

vials containing octreotide (sandostatin) in a dose of 50 microgram on 8 hourly basis for five consecutive days. Endoscopy and sclerotherapy was done in patients when expertise was available.

Those who could not afford octreotide therapy were given assiduous medial care. Outcome measures during their stay in the hospital were survival, death (regardless of the precise cause, was considered

to be related to variceal bleeding), number of blood transfusion, episodes of rebleeding and days with bleeding. Variceal bleeding was considered to have been controlled if the following criteria were met;

- A stable haemoglobin and or haematocrit concentration.
- Stable blood pressure (No reduction in systolic pressure exceeding 29 mm Hg, once the blood pressure had been stabilized).
- Transfusion requirement of no more than two units in a two hour period.

RESULTS

A total of 50 patients were included in this study. The age ranged form 28 to 70 years with a male predominance. Cirrhosis liver of viral aetiology was very common 46 (92%), as compared to other etiological factors. 28 (56%) patients had viral hepatitis C, 17 (34%) had viral hepatitis B and one patients had both B and C type of viral hepatitis. Splenic enlargement was noted in 34 (68%) and hepatomegaly in 10 (36%) cases only. Grade III oesophageal and fundal varices, gastropathy and active variceal bleeding were more common in octreotide group. Number of blood transfusion and duration of stay in the hospital were almost the same in the two groups. (table–I)

A total of 12 (24%) patients died in the hospital. They had bleeding episodes on more than two occasions in the past. All of them had Child's grade C type of liver dysfunction. 9 (18%) patients, of the two groups, died due to massive and prolonged bleeding. Of the non-octreotide group one patient died due to septicemia while 2 cases of the octreotide group died due to hepato renal syndrome. Most of the patients of the two groups, who survived, had Child's grade A and B type of liver dysfunction. (table-II)

DISCUSSION

Variceal haemorrhage complicates the clinical course of chronic liver disease in about 30% of the patients. Mortality for the indexed bleed is as high as 50% with a 30% mortality for subsequent recurrent bleeds. The rate of recurrent haemorrhage in those who survive the initial bleeding episode is as high as 100% over two years.[2]

Various modalities of procedures are recommended for emergency treatment of bleeding oesophageal varices with claims of bleeding control in 60 to 95 percent of cases.[1] However, such facilities are not always available nor is the expertise required to inject a copiously bleeding varix. Occasionally bleeding is so severe that visibility is obscured and at times patients cannot safely undergo endoscopy, without an endotracheal tube because of the dangers of aspiration some times the procedures is delayed because the patient is not stable. These procedures have a failure rate and complications and are not applicable out side the centres where they are actually needed e.g. home, ambulance.[2,3] An important consideration is that the patient is uncomfortable with these procedures and remembers the unpleasant experience for ever. These is always an interval before a specialized procedure can be (which cannot be provided immediately) carried out. Thus the active drug that might "hold" the bleeding in the interval would be of great clinical use. Consequently, if given a choice, most patients with bleeding oesophageal varices would prefer effective vasoactive treatment. It is immediately available and does not require a special skill. There is evidence that patients who continue to bleed or rebleed early are those with high variceal or portal pressures. This suggests that the use of vasoactive drug over several days is of potential therapeutic benefit.[1,2,4]

Since its introduction in 1956 and until recently, vasopressin has remained the vasoactive treatment most widely used for

TABLE – II

BASE LINE CHARACTERISTICS OF 50 PATIENTS WITH ACUTE VARICEAL BLEEDING TREATED WITH OCTREOTIDE OR CONVENTIONAL THERAPY

	GROUP–A	GROUP–B	GROUP–C
NO. OF PATIENTS	12	22	16
PREVIOUS VARICEAL BLEEDING NO. OF PATIENTS	08	06	04
MASSIVE BLEEDING NO. OF PATIENTS	11	04	03
UNCONTROLLED BLEEDING (0-48 HRS) NO. OF PATIENTS	08	03	02
EPISODES OF REBLEEDING NO. OF PATIENTS	05	03	03
ENCEPHALOPATHY	--	--	--
SEVERE	12	03	01
MODERATE	0	01	01
ASCITIS	10	12	09
BILIRUBIN (mg/dl)	04	02	2.5
MEAN/RANGE	(2.1-8)	(1-5)	(1-8)
SGPT (MEAN/RANGE)	160	50	65
	(80-500)	(30-95)	(40-170)
PROTEIN (g/dl)	5.2	3.2	5.8
MEAN/RANGE	(4.9-6)	(5.3-6)	(2-3.5)
ALBUMIN (g/dl)	42	21	20
MEAN RANGE	(22-120)	(1-35)	(16-24)

Group A = Those patients who died in the hospital.

Group B = Octreotide group who survived.

Group C = Non octreotide group who survived.

the control of acute variceal bleeding. Its success rate is less than 50 percent. In addition to doubts regarding its efficacy, vasopressin is associated with side effects in about 25 percent of the patients, several of which require withdrawal of treatment and some of which can be fatal. To minimize the side effects and enhance the vasoactive effects of the drug , two new therapeutic approaches using vasopressin have been proposed. The first entails the use of a vasopressin analogue triclycyl lysine vasopressin (terlipression or glypressin) which has some biological activity in itself but is enzymatically cleaved in vivo to lysine vasopressin. Placebo control trials have shown glypressin to be effective. The second approach entails concomitant admin-

istration of nitroglycerine. The rationale for this treatment is that nitroglycerine does not change the effects of vasopressin on portal pressure, but prevents many of the systemic side effects particularly on the coronary circulation. Controlled clinical trials with glypressin or combined vasopressin nitroglycerine treatment show that these drugs are associated with fewer side effects than vasopressin. An increased efficacy, however, of glypressin or combined vasopressin nitroglycerine treatment over vasopressin alone has not been proved. The magnitude of splanchnic haemodynamic effects in terms of portal pressure reduction is variable, with little effect in some patients.[4]

Recent studies of portal pressure in the first 48 hours after admission for variceal bleeding have shown that "difficult bleeders" that is, those who seem to continue to bleed or have early variceal rebleeding have a higher portal pressure. It was difficult to establish a threshold pressure for an increased risk of "uncontrolled" bleeding but when the hepatic venous pressure gradient fell to below 16 mm Hg, there was a much smaller risk of rebleeding. Studies of intravariceal pressure show that it clearly varies with central venous pressure and lower pressure results in less early rebleeding. In stable cirrhotic patients (not bleeding) octreotide has little or no effect on wedged hepatic venous pressure.[4] In published studies the effect of octreotide on portal pressure is variable. Nevens and his colleague reported that variceal pressure changes after injection of octreotide were variable and that the mean change in pressure did not reach a statistical significant.[5] Thus it is obvious that this drug has a doubtful role to control an acute variceal bleeding episode.

There is a strong correlation between variceal size, colour (Red spots), assessed endoscopically, and the probability of imminent haemorrhage. Child's grade is used to assess hepato cellular function in cirrhosis. It correlates with variceal size and with the presence of red signs. It is the most important predictor of the likelihood of bleeding and is independently associated with a high risk of rebleeding. A child ugh's C patients together. The number of blood transfusions required before the initial endoscopy, for an episode of variceal bleeding, is correlated with the severity of liver dysfunction and survival. It has been reported that with the use of somatostatin 57 percent of those within child's grade C will not have their bleeding controlled.[6,7] As somatostatin and octreotide do not play any role to improve liver dysfunction, its use in variceal bleed which is closely related to its grading, needs further trials.

A trial by Valenzvella et al suggested that somatostatin is no more effective than placebo. They and Terblanche et al, in two separate studies, reported that the bleeding often stops spontaneously in 60 to 83 percent of the patients.[1,8] Peter CG and his colleagues, in a double blind study and meta analysis, comparing somatostatin with placebo, were unable to show a clinical benefit of somatostatin in the emergency treatment of bleeding oesophageal varices.[1] In our patients success was surprisingly high in non octreotide group, perhaps due to the assiduous medical care these patients received as part of clinical protocol. No placebo controlled trials have been performed with octreotide.

Octreotide (sandostatin) is an expensive drug. A single vial of 50 microgram costs about 212 rupees. When given on 8 hourly basis for 5 days for the control of single episode of bleeding, amounts to 3180 rupees. In Hong Kong a 5 day course of octreotide costs about US$ 1940.[9] The cost of vasoactive drug in the western world is expensive as well. In the UK approximately 6.1 million pounds of NHS resources are devoted to the treatment of 3000 acute hospital admission for variceal bleeding every year. Vasoconstrictors like vaso-

pressin may save approximately 36 lives per annum for an additional 145 thousand pounds. If this drug is administered with intravenous glyceryl trinitrate, it increases the over all cost by 582 thousand pounds to a total of 6.7 million pounds. Thus to spend such a large amount vasoconstrictor like octreotide should be carefully assessed to determine their potential clinical and economic benefit.[10]

Alongwith the common adverse effects of octreotide, such as pain at the injection site and nausea, less frequent effects, such as cholelithiasis, gallbladder hypercontractability and gastritis have been described. More dreadful complication include deterioration in glomerular filtration rate leading to hepatorenal syndrome, and increase in the intestinal transit time inducing the onset of encephalopathy.[7,11]

In our study, in all the patients who survived, the number of blood transfusions required and the duration of their stay in the hospital, between the two groups, were similar. We failed to show any beneficial role of the octreotide over conventional therapy. However, in our patients, the mortality rate was higher in the octreotide group. The mortality was also higher in two separate studies by Valenzvella and Burrough et al.[1] This may be due to an adverse effect of the drug still not documented.

New treatments of gastro oesophageal varices are usually variants of the old. Their proponents are initially enthusiastic, but over the subsequent decade each method takes its place in the back ground with its forebears. Clinical trials must be interpreted consciously, the time of patients being entered, the aetiology of cirrhosis and of the portal hypertension together with the degree of hepatocellular failure (how many childs C grade?) must be noted. The time of randomization is very important. The risk of further haemorrhage and death rapidly diminishes as the patient survives the first few days after a bleed.

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