ORIGINAL ARTICLE

EARLY INITIATION OF BETA BLOCKERS FOLLOWING PRIMARY ENDOSCOPIC THERAPY FOR BLEEDING OESOPHAGEAL VARICES IN CIRRHOTICS

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Background: Beta-blockers provide secondary prophylaxis following endoscopic therapy for variceal bleeding. Guidelines recommend starting beta-blockers 6 days after endoscopy to prevent masking hemodynamic signs of re-bleeding. We aimed to see safety of earlier initiation of beta-blockers. **Methods:** Cirrhotic patients with upper GI bleed were given intravenous vasoactive agents until undergoing endoscopy. Patients with only oesophageal varices as source of bleed were recruited. Vasoactive agents were discontinued following variceal banding. The patients were observed for 12–18 hours, discharged on oral carvedilol 6.25 mg BID and monitored for 6 weeks for re-bleeding and mortality. **Results:** Fifty patients were included, 27 (54%) male and 23 (46%) female. Average age was 43±3 years. Aetiology of cirrhosis was HCV in 42 (84%), HBV in 6 (12%), HCV & HBV in 2 (4%) and indeterminate in 1 (2%) patient. Seventeen (34%) patients had Child A, 22 (44%) Child B and 11 (22%) had Child C disease. Hospital stay was under 24 hours in 24 (48%), 24–48 hours in 15 (30%) and 48–72 hours in 11 (22%) patients. Five (10%) patients underwent EGD within 6 hours of admission, 28 (56%) within 12 hours, 14 (28%) within 24 hours and 3 (6%) within 36 hours. No re-bleeding, mortality or drug related adverse effects were noted during 6 weeks after discharge. **Conclusions:** Our study proves possibility of shorter management of variceal bleeding by having a 12–18 hour monitoring after endoscopic banding, followed by beta-blocker initiation and discharge. This will safely reduce physical and financial burden on health services.

Keywords: Liver cirrhosis; Portal hypertension; Variceal bleeding; Beta-blockers

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INTRODUCTION

The commonest complication of liver cirrhosis is portal hypertension. Portal hypertension leads to the formation of a portosystemic collateral circulation, with subsequent development of gastroesophageal varices, ascites, encephalopathy, and recurrent infection.[1] Ascites is the most common complication of cirrhosis, and 60% of patients with compensated cirrhosis develop ascites within 10 years during the course of their disease.[2] Oesophageal variceal bleeding is the most serious complication of liver cirrhosis with portal hypertension. Gastroesophageal varices are present in approximately 50% of patients with cirrhosis.[3] Their presence correlates with the severity of liver disease.[4] While around 35% of Child A patients have varices, they are present in almost 70% of Child C patients.[5] Various endoscopic treatment modalities to treat varices are band ligation and injection sclerotherapy. These endoscopic methods are extremely effective in controlling acute variceal bleeding and are also used as secondary prophylaxis.[6] Sclerotherapy is not recommended for primary prophylaxis because of inconsistency of results across trials.[7] EVBL has been shown to decrease the risk of first bleeding by 64% and mortality by 45% when compared to no treatment.[8] Beta-blockers such as propranolol and carvedilol are used for secondary prophylaxis against oesophageal variceal bleeding.[9]

Propranolol lowers cardiac output (via blockade of beta-1 adrenoreceptors) and causes splanchnic vasoconstriction (via blockade of vasodilatory adrenoreceptors of the splanchnic circulation), reducing portal and collateral blood flow. Carvedilol possesses both nonselective β-antagonist and α1-receptor antagonist activity and has been used in the management of portal hypertension.[10] In such cases it is standard practice to start beta-blockers after 5 days/120 hours following primary endoscopic therapy. According to studies, the risk of rebleeding following primary endoscopic therapy plus vasoactive agents is greatest during the initial 5 day/120-hour period.[9] The Baveno consensus recommends starting beta-blockers from day 6 after initial endoscopy. The rationale for starting beta-blockers after day 5 is to reduce the risk of masking hemodynamic signs of re-bleeding. At our centre, it is usual practice to treat patients who have bleeding oesophageal varices with a shorter vasoactive agent regimen than the recommended 3–5 days. Therefore, we also initiate beta-blockers as secondary

prophylaxis before the recommended 5-day/120-hour window. In our experience, it has proven to be safe and has resulted in shorter hospital stay and has translated into decreased cost of treatment with no increase in mortality.

Our aim in this study was to see the safety and efficacy of early initiation of beta-blockers before day 6 following endoscopic therapy for secondary prophylaxis of variceal bleeding. Our working hypothesis was that it would be safe to use beta-blockers during the initial five-day period following primary endoscopic therapy in a patient with bleeding oesophageal varices.

MATERIAL AND METHODS

This was a quasi-experimental study and was carried out at the Department of Gastroenterology & Hepatology, Shaikh Zayed Hospital, Lahore from 1st May to 31st July 2015. The study was initiated after obtaining approval from institutional review board. All adult patients aged 18 years and above with a history of liver cirrhosis presenting to our hospital with upper GI bleed (manifest as hematemesis or malena or both) were administered vasoactive agents. These were either terlipressin, at a dose of 2mg I.V stat followed by 1mg 6 hourly, or octreotide, at a dose of 50 micrograms per hour infusion. All patients had nasogastric intubation and lavage to check for the presence of active bleeding. Nasogastric lavage was done with water until clear outflow was seen. All patients also received intravenous omeprazole 40 mg 12 hourly along with intravenous ceftriaxone 1 gram administered once daily. Patients with hepatic encephalopathy also received intravenous metronidazole, lactulose enemas and a higher dose of ceftriaxone of 1 gram 12 hourly. The patients underwent upper GI endoscopy after ensuring airway and hemodynamic stability, adequate conscious level and receiving blood transfusion if the latter was required to bring haemoglobin level to at least 7 g/dL, as per Baveno recommendations. Once oesophageal varices were confirmed as the only source of bleed, band ligation was done. Patients with Other sources of bleeding in addition to oesophageal varices such as gastric varices and ulcers were not included in our study. Written and informed consent was obtained from all patients. A total of 50 patients were included. Vasoactive agents were stopped after endoscopic band ligation. The patients were monitored for a period of 12–18 hours after EVBL. Patients who were stable at the end of the observation period were discharged home on the beta-blocker carvedilol at a dose of 6.25 mg 12 hourly after ensuring that no contraindications to beta-blocker therapy were present. All patients also received oral ciprofloxacin 500mg BID for a period of 5 days on discharge. The patients were monitored for the occurrence of re-bleeding for six weeks following initial endoscopic therapy. Re-bleeding was defined as an episode of clinically significant bleeding from portal hypertensive source, occurring after initial endoscopic control of bleeding during admission or during the 6-week monitoring period following discharge. Clinically significant re-bleeding meant recurrent melena or hematemesis resulting in hospital admission, blood transfusion or 2 g or higher drop in haemoglobin during the 6-week monitoring period. Mortality was checked at six weeks following initial endoscopic therapy. Monitoring was done via telephone contact, which was done on a weekly basis. All patients were recalled for repeat endoscopy after two to three weeks of initial endoscopic treatment. Band ligation of varices was repeated at this visit if deemed necessary on endoscopic observation.

The SPSS-22 was used to analyse the data. Variables included age, sex and efficacy. Nominal data (sex and efficacy) was represented as frequency percentages. Numerical data (age) was represented as mean±standard deviation. We routinely prescribe beta-blockers before the usual recommended 5-day period at our Department. We have not observed any adverse outcomes as a result of this policy. Therefore, this will not be an added risk to our patients.

RESULTS

A total of 50 patients were included in the study out of which 27 (54%) were males and rest of 23 (46%) were females. The mean age of the patients was 43±3 years. The predominant cause of liver cirrhosis was hepatitis C infection with 42 (84%) patients affected. Other causes were hepatitis B, hepatitis B & C co-infection and indeterminate causes (Table-1). Severity of liver disease in the study population was evaluated using the Child-Turcotte-Pugh score. The largest number, 22 (44%) patients, were in Child class B, followed by Child class A and C respectively (Table-2). Hospital stay was under 24 hours in almost half (24 patients, 48%) of our patients. The remaining patients were discharged within 48–72 hours of admission (Table-3). The time interval between admissions to emergency with GI bleed to undergoing endoscopy was an important factor. Thirty-three (66%) patients were able to undergo endoscopy within 12 hours of arriving in emergency. Most of the remaining patients underwent endoscopy within 24 hours of admission. 3 patients had a delayed endoscopy beyond 24 hours. These were scoped within 36 hours of admission (Table-4). In our observation, cause of delay in endoscopy beyond 24 hours was blood transfusion requirements in 2 patients and encephalopathy in one patient. No re-bleeding or mortality was noted after 6 weeks of initial endoscopic therapy. No drug related adverse effects were reported.

Table-1: Aetiology of liver disease

Cause of Liver Cirrhosis			
HCV	**HBV**	**HCV & HBV**	**Unknown**
42 (84%)	5 (10%)	2 (4%)	1 (2%)

Table-2: Stage of liver disease

Child Class		
A	**B**	**C**
17 (34%)	22 (44%)	11 (22%)

Table-3: Duration of inpatient stay

Hospital Stay		
<24 hours	**24–48 hours**	**48–72 hour**
24 (48%)	15 (30%)	11 (22%)

Table-4: Delay between presentation to A&E and EGD

Time interval			
Within 6 hours	**Within 12 hours**	**Within 24 hours**	**Within 36 hours**
5 (10%)	28 (56%)	14 (28%)	3 (6%)

DISCUSSION

Current guidelines for oesophageal variceal bleeding in cirrhotic patients recommend a 3–5 day vasoactive drug duration followed by initiation of beta-blocker therapy at day 6, which entails a hospital stay of at least 5 days.[8] This is due to the expected high risk of re-bleeding especially during the first 120 hours following endoscopic haemostasis. It is thus expected that the lowering of blood pressure induced by beta-blocker therapy may mask the hypotension caused by bleeding and resultant hypovolemia.

Our study shows that much shorter management is possible for such patients by administering vasoactive agents only prior to endoscopic band ligation. These agents must be continued till the patient is deemed fit to undergo endoscopic treatment.

In cases where uncontrolled "torrential" bleeding is experienced, either during initial nasogastric lavage, or during endoscopy, Sengstaken-Blakemore tube placement with pressure tamponade of bleeding varices is a viable therapeutic option.[11] The tube is kept in situ with balloons inflated for 24 hours. After 24 hours, the tube is removed and endoscopy is performed. In our study group, no patient required balloon tamponade.

Transjugular intrahepatic shunt (TIPS) is a known treatment option in the management of patients whose bleeding is uncontrolled by conventional means such as vasopressor agents and endoscopic therapy.[12] However, it is rarely used at our centre and even in the most aggressive bleeders, we are able to successively achieve haemostasis using vasoactive agents, endoscopic therapy and balloon tamponade using Sengstaken Blakemore tubes. Altered sensorium in actively bleeding patients makes them uncooperative for endoscopic procedures. Such patients ideally require sedation and intubation of airway in order to avoid aspiration of gastric contents.[13] It is not standard practice at our centre to sedate and intubate patients with encephalopathy and perform EGD. Hence in patients with encephalopathy, endoscopy is done only after encephalopathy has improved to at least Grade I (as assessed on the basis of West Haven criteria). Encephalopathy is managed with the standard regime of antibiotics (cephalosporins and metronidazole), lactulose (orally and enemas), branched chain amino acids and L-ornithine L-aspartate.[16]

The time period between presentation to emergency and undergoing endoscopy is what we call the "door to endoscopy time". This depends on a stable hemodynamic status, adequate haemoglobin levels (at least 7 g/dL) and a satisfactory conscious level.[8]

Once definitive endoscopic therapy has been performed, the patients can be monitored for a period of approximately 12 hours. If stable at the end of monitoring period, patients can be discharged on oral beta-blockers. Our experience confirms the high efficacy of combined vasoactive agents coupled with endoscopic therapy in achieving primary haemostasis. It also shows the safety of early discharge and initiation of beta-blockers for secondary prophylaxis. Strict follow up, especially for repeat endoscopy two weeks after primary endoscopy, is mandatory. This will serve to reduce physical and financial burden on health services by allowing quicker turnover of admitted patients with no increase in morbidity or mortality.

While we advocate the use of this policy in all patients, we also recognize that patients with advanced liver cirrhosis represent a dynamic population with clinical issues affecting multiple systems. Of these issues, the most commonly encountered are hepato-renal syndrome, spontaneous bacterial peritonitis, and hepatic encephalopathy.[14, 15] In many cases the patient presenting to the emergency with variceal bleeding may well have one or more of these conditions. The initial assessment of cirrhotic bleeders hence also involves tests such as assessment of renal function and diagnostic (plus therapeutic, if necessary) ascitic fluid paracentesis plus any other investigations that the clinical condition dictates. The management of patients with any of these conditions requires further measures in addition to those for managing variceal bleeding. This management requires modalities such as intravenous albumin, culture specific antibiotics etc. Hence, the above practice of a short and efficient management of the oesophageal variceal bleeder can only be done in cases when the aforementioned (or any other) clinical conditions are not present. In case

they are present, management definitely entails longer hospital stay and specific workup and treatment. We were fortunate in our study as to not encounter significant parallel pathologies in our patients except for one who had encephalopathy. We were therefore able to exercise our management plan efficiently.

CONCLUSION

Patients who remain stable for a period of approximately 12 hours following endoscopic band ligation for oesophageal variceal bleeding can be safely initiated on beta-blockers and discharged without any increase in morbidity and mortality.

AUTHORS' CONTRIBUTION

AS: Contributions to experimental conception and design. Acquisition, analysis and/or interpretation of data. Writing of article. Drafting the article & revising it critically for important intellectual content. KM: Drafting the article & revising it critically for important intellectual content. MJA & UB: Acquisition, analysis and/or interpretation of data. AK & AA: Writing of article. Drafting the article & revising it critically for important intellectual content.

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