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Endoscopic management of acute oesophageal variceal bleeding within 12 hours of admission is superior to 12–24 hours

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ABSTRACT

Background: Acute oesophageal variceal haemorrhage (AOVH) is a medical emergency. The American Association for the Study of Liver Diseases recommends endoscopy management as soon as possible and not more than 12 hours after presentation. The United Kingdom guidelines recommended endoscopy for unstable patients with severe acute upper gastrointestinal bleeding immediately after resuscitation and within 24 hours of admission. We aimed to evaluate the outcome of endoscopic management of AOVH in less than 12 hours compared to 12–24 hours post admission.

Methods: 297 patients with AOVH were divided into groups depending on the timing of the endoscopic management: 180 within 12 h of admission and 117 patients at 12–24 hours of admission. Routine clinical and laboratory data were collected.

Results: Compared to patients with endoscopic management at 12–24 hours (mean 16 hours), patients with endoscopic management within 12 hours (mean 8.3 hours) of admission had fewer hospital stay days ($P = 0.001$), significant reduction of ammonia levels ($P < 0.0001$) and significant improvement in associated hepatic encephalopathy grade 25 ($p = 0.048$). There were no major clinical events in the 12-hour group, but 8 events in the 12–24 hour group ($p < 0.01$).

Conclusion: Endoscopic management of acute variceal bleeding within 12 hours of admission is superior to endoscopic management at 12–24 hours of admission regarding reduction of hospital stay, ammonia levels, correction of hepatic encephalopathy, re-bleeding and mortality rate, hence, reducing the cost of treatment benefiting patient satisfaction and improving hospital bed availability.

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Acute oesophageal variceal haemorrhage; endoscopic management; hepatic encephalopathy; hospital stay days; portal hypertension

Introduction

Portal hypertension is a leading consequence of cirrhosis and is responsible for the majority of its complications. These include gastrointestinal bleeding from spontaneous rupture of oesophageal or gastric varices, encephalopathy, and ascites [1–4]. Acute oesophageal variceal haemorrhage is a medical emergency with a high incidence of complications and high mortality and therefore, requires intensive care [1]. Variceal haemorrhage is the aetiology of about 70% of all upper gastrointestinal bleeding attacks in patients with portal hypertension. It remains one of the most severe and immediate life-threatening complications in patients with cirrhosis [5]. The aim of the therapy in these patients is to control bleeding, to prevent early recurrence (within 5 days) and prevent 6-week mortality, which is considered, by consensus, the main treatment outcome [6]. When acute variceal haemorrhage is suspected, initial therapy should be focused on restoring volaemia [7], vasoactive drugs during transfer to hospital and maintained afterwards for 2–5 days [8], and antibiotic prophylaxis [1]. Once blood volume restitution has been initiated and haemodynamic stability has been achieved, upper endoscopy should be performed.

The association between endoscopy timing and morbidity-mortality has not been clearly investigated. Current American guidelines recommend that endoscopy should be performed as soon as possible (within 12 hours of admission) in cirrhotic patients with acute oesophageal variceal haemorrhage [2]. UK guidelines on the management of variceal haemorrhage in cirrhotic patients recommend that endoscopy for unstable patients with severe acute upper gastrointestinal bleeding should be performed immediately after resuscitation and within 24 hours of admission to all other patients with upper gastrointestinal bleeding [9]. However, this recommendation appears to be based on 'expert opinion', rather than on the level of evidence, which is in fact very low. For example, one survey showed significant variability in gastroenterologists' opinion of the timing of emergency endoscopy following variceal bleeding [10]. Moreover, there is little related research to date to support this

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current recommendation of endoscopy within 12 h of hospital arrival [11,12]. We hypothesised that endoscopic management of acute oesophageal variceal haemorrhage at 12 hours is superior to endoscopic management at 24 h of admission.

Methods

We tested our hypothesis on 297 cirrhotic patients with upper gastrointestinal bleeding admitted to Tropical Medicine Department, Mansoura Emergency hospital, Gastroenterology and Hepatology Department (Damietta Cardiology and Gastroenterology centre), and Department of Tropical Medicine, Menoufia University, Egypt from February 2020 to May 2020. All patients were subjected to endoscopic examination (under midazolam sedation) and endoscopic variceal band ligation in addition to standard conservative therapy (plasma volume expanders, blood transfusion, vasoactive drugs, and ceftriaxone (1 g/24 hours)). All endoscopic interventions in both groups were performed by highly trained, equally qualified endoscopists.

All patients were subjected to full thorough history taking and laboratory investigations, including total bilirubin, albumin, creatinine, sodium, potassium, haemoglobin levels, leukocytic count, platelet count, prothrombin time, and international normalized ratio (INR). Abdominal ultrasonography was done to determine liver cirrhosis, ascites, portal hypertension and collaterals. The arterial ammonia concentration was determined by the ammonia test Kit II for the Pocket Chem BA device (Arkay Inc., Kyoto, Japan). The blood samples were collected and placed on ice and then were tested within 2 minutes of collection. The continuous measurement range is 8 ~ 285 μmol/litre and the normal blood ammonia level for healthy adults for this device is <54 μmol/litre. Estimated GFR (eGFR) was calculated using the chronic kidney disease epidemiology equation (CKD-EPI) formula. The CKD-EPI equation is a single equation in which values are expressed in ml/min/1.73 m^2 [13].

Exclusion criteria were patients unable to tolerate endoscopy, suffering from cerebral palsy or manifestations of neurological disease, who cannot tolerate sedation, who have severe co-morbidities, e.g., recent myocardial infarction, cardiopulmonary instability, hypertensive shock failing to stabilize after initial resuscitation, prior to esophagogastroduodenoscopy and age <18 yr. Also, patients who had withdrawn their informed consent to participate in the study or their first degree relatives, those who refuse the procedure or the endoscope. Moreover, patients with causes of upper GIT bleeding other than ruptured oesophageal varices, e.g., isolated gastric varices, malignancy, portal hypertensive gastropathy. The endpoints were the control of bleeding and hospital discharge. The patients or first degree relative signed written informed consent to participate in the study. The study was approved by the Mansoura Institutional Ethics and Investigation Committees.

Data were analysed using SPSS version 22. Analysed data are shown as median (IQR) or mean [SD]. For analysis of quantitative data, T-test was used for comparison between the two groups and paired t-test was used to compare parameters in the same group. To compare qualitative data, $\chi 2$ test was used. Mann–Whitney U test for continuous variables. $P < 0.05$ was considered significant at 95% confidence interval.

Results

The 297 patients were classified into two groups whose endoscopic band ligation was performed within 12 hours post-admission (8.3 [2.4] hours) and those where it was performed within 12–24 hours (16.0 [2.5] hours, $p < 0.001$). Table 1 shows the demographic, clinical and laboratory data of study patients. There were no significant differences between groups as regards age, sex, aetiology of liver disease, Child–Pugh

Table 1. The demographic, clinical and laboratory data.

Parameters	Endoscope within 12 hours N = 180	Endoscope between 12–24 hours N = 117	P value
Age/years	61.3[8.6]	59.6[5.3]	0.25
Sex (m/f)	121/59	69/48	0.32
HCV related cirrhosis	170/180	110/117	0.87
HBV related cirrhosis	7/180	5/117	0.86
NASH related cirrhosis	3/180	2/117	0.97
Child–Pugh score (N): A/B/C	12/46/122	12/18/87	0.083
Encephalopathy grade (N): Normal/grade 1	151/29	99/18	0.86
Transfusion units	1(0–2)	1(0–2)	0.825
eGFR using (EPI) (mL/min/1.73 m^2)	52 [14.4]	54 [13.5]	0.11
Albumin (g/L)	29 [0.9]	27 [0.2]	0.39
Bilirubin (μmol/L)	14.1 [6.2]	12.4 [6.2]	0.50
ALT (U/l)	62 [17.2]	61 [21.1]	0.77
AST (U/l)	46.3 [13.3]	56.2 [12.5]	0.75
INR	1.7 [0.41]	1.7 [0.3]	0.50
Platelet (10^9/L)	83 [23.8]	82 [28.6]	0.81
WBC (10^9/L)	12 [4.1]	11[3.4]	0.98
Haemoglobin (g/L)	79 [26]	78 [23]	0.61
Arterial ammonia (umol/L)	81 [12.3]	78 [12.3]	0.97

Data mean [SD], median (IQR) or n (%). ALT, Alanine aminotransferase; AST, aspartate aminotransferase; eGFR (EPI): estimated glomerular filtration rate using epidemiology equation; INR, international normalised ratio; WBC, white blood cells.

Table 2. Post-treatment versus pre-treatment changes in the laboratory and clinical data.

	Endoscope within 12 hours N = 180			Endoscope between 12–24 hours N = 117		
	Before	After	P value	Before	After	P value
eGFR (mL/min/1.73)	52 [14.4]	65 [9.5]	<0.001	54[13.5]	64[10.5]	<0.001
Haemoglobin (g/L)	79 [26]	87[27]	0.001	78 [23]	82[21]	0.001
WBC (10^9/L)	12.1 [4.1]	11.5 [2.1]	0.42	11 [3.4]	11.1 [2.2]	0.86
Arterial ammonia (umol/L)	82 [12.3]	48 [12.2]	<0.001	78 [12.3]	58 [15.1]	<0.001
Encephalopathy grade (N): Normal/G1	151/29	176/4	0.001	99/18	109/8	0.037
Post-endoscopy hospital stay (days)		2 [0.79]			4.9 [1.05]	0.001

eGFR: estimated glomerular filtration rate. WBC: white blood cells. Data mean [SD] or n (%).

score, grade of hepatic encephalopathy, transfusion units, platelet count, bilirubin, serum albumin, ALT, AST levels, INR, serum creatinine, WBC, haemoglobin, and arterial blood ammonia.

Table 2 shows post-treatment versus pre-treatment changes in the laboratory and clinical data in both groups. In both groups, compared to pre-treatment data there were a significant improvement in eGFR, haemoglobin, arterial ammonia levels and hepatic encephalopathy grade but no significant change in the WBC. The relative change in the eGFR ($p = 0.94$), haemoglobin ($p = 0.90$), and WBC ($p = 0.28$) did not differ between the groups. However, endoscopy <12 hours produced a greater fall in ammonia ($p < 0.001$), an improved encephalopathy grade ($p = 0.048$), and a shorter hospital stay. Of those in the 12–24 hours group, there were eight major events: four cases of re-bleeding, two deaths, one acute on top of chronic liver failure and hospital-acquired pneumonia. There were no such major events in those managed <12 hours from admission ($p < 0.001$).

Discussion

Although current guidelines recommend performing endoscopy within 12 hours for acute variceal bleeding [2,9], the optimal timing remains controversial and the available evidence has been limited and generally of very low quality [14]. Studies examining the influence of timing of endoscopy failed to demonstrate any advantage of endoscopy before 12 hours, moreover, very early endoscopy may lead to poorer outcomes [15]. In testing the hypothesis that endoscopy within 12 hours of admission is superior to longer than 12 hours, we report that former is associated with a reduction in hospital stay, a more rapid fall in arterial ammonia, and a more rapid improvement in encephalopathy with fewer major clinical events.

Previous studies recommended that, awareness of key cost drivers in the treatment of AOVH can allow healthcare providers to recognize ways for cost decrease. For example, a large UK study has revealed that more timely endoscopy for acute upper gastrointestinal bleeding can decrease hospital inpatient stay (accountable for 60% of in-hospital costs for these patients) by an average of 1.7 days [16]. These results match our study in that early endoscopic treatment of AOVH reduces the hospital, staying days and hence the cost of treatment. Furthermore, Garg et al. found that early oesophagogastroduodenoscopy (OGD) was associated with a shorter hospital stay (4.6 days vs. 8.5 and 7.6 days for late and no intervention, respectively) and lower hospitalization costs (~US$28k lower vs. late endoscopy and US$25k lower vs no endoscopy) [17].

Early OGD has been previously found to reduce the risk of recurrent bleeding, transfusion requirements [18]. However, a study of over 4000 patients in the UK found no improvement in mortality or need for surgery in patients who underwent early (<12 hours) endoscopy, though, they did have a shorter length of stay and there was a trend towards lower re-bleeding rates [16]. Acknowledging the small sample size (and therefore weakness), we nevertheless point to eight major events in our patients managed 12–24 hours after admission, but none in those managed within 12 hours.

Renal function is a critical prognostic factor in cirrhotic patients with oesophageal variceal bleeding [19]. Bleeding may predispose to kidney hypoperfusion and impaired renal function [20]. We found a significant improvement in eGFR in both groups compared to the pre-treatment levels, but not between groups. Garg et al. found a lower rate of complications, such as renal failure and respiratory failure in patients who underwent early endoscopy [17]. These results could be explained by the use of antibiotics and splanchnic vasoconstrictors (somatostatin or terlipressin) in both groups. Previous studies had documented that terlipressin has superior evidence in improving renal impairment in cirrhotic patients [21,22].

Ammonia is a key factor in the pathogenesis of hepatic encephalopathy: a synergistic effect between systemic oxidative stress and ammonia is implicated [23,24]. The presence of blood in the upper gastrointestinal tract is the main source for increased ammonia and nitrogen absorption from the gut, also, blood transfusions may result in mild haemolysis, with resulting elevated blood ammonia levels [25]. In our study, there was a significant reduction in ammonia levels in both groups after treatment versus before treatment. This could be attributed to either reduction of gastrointestinal bleeding or to complete stoppage of bleeding, especially in early endoscopic management groups, as we noticed that there was a no significant difference between both studied groups as regard blood transfusion or infection. Importantly, the study

demonstrated that the reduction of arterial ammonia levels was more significant in early endoscopic treated group at 12 hours in comparison to 12–24 hours endoscopic treated group, indicating that the early endoscopic management of acute variceal bleeding is superior to delayed treatment in stopping the bleeding which is the main source of ammonia in our patients [26].

Hepatic encephalopathy is a common consequence of liver cirrhosis [27]. Although there is an improvement in hepatic encephalopathy in both groups post-treatment, the results of this study showed an improvement in hepatic encephalopathy following endoscopic treatment at 12 hours post presentation versus endoscopic treatment at 12–24 hours-post presentation. These results could be explained by early cessation of bleeding and a reduction of the ammonia levels, the key factor of hepatic encephalopathy with early endoscopic treatment [28]. We speculate that early management with control of bleeding is the main source of ammonia with consequent reduction of the ammonia level that is responsible for the improvement of hepatic encephalopathy. This supports the view that early endoscopic management of acute variceal bleeding according to guidelines is an important measure to improve morbidity. Accordingly, we agree with Barkun et al. [29], who recommended early endoscopy to decrease morbidity and mortality, although some suggested that the time to endoscopy was not a significant predictor of outcome in patients with variceal bleeding [15].

A limitation of this study is the majority of studied patients had viral-related cirrhosis (chronic HCV infection and chronic HBV infection), so our finding may not necessarily be extrapolable to other aetiologies. Nevertheless, our data are an advance in biomedical science as it shows that endoscopic management of AOVH within 12 hours of admission is superior to management at 12–24 hours of admission.

Summary table

What is known about this subject?

- Acute esophageal variceal haemorrhage (AOVH) is a medical emergency.
- There is a scientific debate about which is better: performing endoscopy as early as possible or waiting till the patients is completely resuscitated and stabilized.

What this paper adds

- Endoscopic management of acute esophageal variceal bleeding within 12 hours of admission is superior to endoscopic management at 12–24 hours of admission regarding reduction of hospital stay, ammonia levels, correction of hepatic encephalopathy, re-bleeding and mortality rate.

Disclosure statement

No potential conflict of interest was reported by the authors.

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