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Original Article

A controlled trial of early versus delayed feeding following ligation in the control of acute esophageal variceal bleeding

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Abstract

Background: The impact of feeding after endoscopic treatment of gastroesophageal varices has rarely been thoroughly investigated. We conducted a controlled study to evaluate whether delayed feeding causes a reduced incidence of rebleeding on patients receiving emergency endoscopic therapy for bleeding gastroesophageal varices.

Methods: Cirrhotic patients presenting with acute esophageal variceal bleeding were provided critical treatment through emergency endoscopic variceal ligation. After bleeding from the varices had been arrested, the eligible participants were randomized to two groups. The early-feeding group and the delayed-feeding group were asked to fast for 4 hours and 48 hours, respectively, after endoscopic therapy. The primary end points were initial hemostasis, very early rebleeding, and ulcer-bleeding rates.

Results: There were 36 patients enrolled in the early-feeding group and 34 patients in the delayed-feeding group. Both groups were comparable in baseline data. Initial hemostasis was achieved in 100% in both groups, and very early rebleeding was not encountered in either group. The incidence of adverse events was similar between both groups. The mean hospitalization days were 6.0 ± 2.4 days (range: 2–17 days) in the early-feeding group, and 7.5 ± 3.1 days (range: 3–22 days) in the delayed-feeding group ($p < 0.05$).

Conclusion: Early feeding with liquid diet after a successful endoscopic therapy of bleeding varices did not have any impact on hemostasis.

Keywords: banding ligation; early feeding; variceal bleeding

1. Introduction

Acute esophageal variceal hemorrhage is a formidable complication of portal hypertension, although its management has evolved rapidly in recent years.[1,2] Vasoconstrictors are generally used as a first-line therapy. Following the use of a vasoconstrictor, endoscopic therapy is often employed to arrest the bleeding varices as well as to prevent early rebleeding. A meta-analysis showed that the combination of vasoconstrictor and endoscopic therapy is superior to endoscopic therapy alone in the control of acute esophageal variceal hemorrhage.[3] Previous studies showed that endoscopic variceal ligation (EVL) is superior to endoscopic injection sclerotherapy (EIS) in the control of active variceal hemorrhage.[4,5] It is thus recommended that EVL is the endoscopic treatment of choice for acute esophageal variceal bleeding.[5] Moreover, apart from the control of acute variceal bleeding, the use of prophylactic antibiotics has been proven to be helpful in the prevention of bacterial infection as well as early variceal rebleeding.[6] Currently, the combination of vasoconstrictors, prophylactic antibiotics, and EVL has become the standard of therapy for patients with acute esophageal variceal bleeding.

On the other hand, a high incidence of early rebleeding may be encountered after combination therapy. It is estimated that

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40% of early rebleeding occurs within 5 days of initial bleeding, which in turn leads to a high mortality rate.[7,8] The impact of feeding after endoscopic treatment of gastroesophageal varices has rarely been well investigated. It is still unknown whether those early rebleeding events have any relation to the feedings of patients with acute esophageal variceal bleeding treated with EVL. It is customary for clinicians to institute absolute fasting for 2 or 3 days after an emergency EVL. This may presumably be a safe approach to guard against the occurrence of early rebleeding. However, prolonged fasting may be unethical to patients who have a low risk of rebleeding. Moreover, prolonged fasting may lead to impaired nutrition and development of ascites in cirrhotic patients, possibly resulting in an increased length of hospitalization. Thus, we conducted a controlled study to evaluate whether delayed feeding has a reduced incidence of rebleeding on patients receiving emergency endoscopic therapy for bleeding gastroesophageal varices.

2. Methods

Between March 2011 and December 2012, patients presenting with acute gastroesophageal variceal bleeding proven by emergency endoscopy within 12 hours were considered for enrollment. Other enrolled criteria were (1) the etiology of portal hypertension was cirrhosis; (2) patients between 20 and 80 years of age; (3) EVL was performed after confirmation of acute esophageal variceal bleeding, and Histoacryl injection was performed if acute gastric variceal bleeding was diagnosed; and (4) variceal bleeding was arrested on the spot by emergency endoscopic therapy.

Acute esophageal variceal bleeding was defined as (1) when blood was directly seen by endoscopy to issue from an esophageal varix (active bleeding), or (2) when patients presented with red color signs or blood clots on their esophageal varices with blood in the esophagus or stomach, and no other potential site of bleeding has been identified (inactive bleeding).[8] *Gastric variceal bleeding* was defined as active spurting from a gastric varix or the presence of red spots and erosions on a gastric varix.[9] The diagnosis of cirrhosis was based on history, physical examinations, liver histology, or image studies. Our methods of emergency EVL and Histoacryl injection have been described previously in detail.[8–10] Briefly, ligation was initiated at the bleeding point, hematocystic spots or white nipple signs if present, or at gastroesophageal junction, and advanced proximally. The obturation agent for gastric varices was 0.5 mL *n*-butyl-2-cyanoacrylate (Histoacryl; B. Braun Melsungen AG, Melsungen, Germany) mixed with 0.5 mL Lipiodol Ultra-Fluide (Guerbet, Bois Cedex, France). The injection sites were focused at either the bleeding site or the hematocystic spots, or the erosive spots on the culprit varix. After completion of EVL or gastric variceal obturation, water irrigation was performed to ensure hemostasis was achieved.

The exclusion criteria were (1) association with a severe systemic illness, such as sepsis, uremia, advanced hepatocellular carcinoma (HCC), and HCC staging > Barcelona-Clínic Liver Cancer B; (2) failure to control variceal bleeding by emergency endoscopic therapy; (3) uncooperative or on endotracheal intubation; (4) ever received EIS or EVL within 1 month prior to index bleeding; (5) Child–Pugh's scores >13; (6) deep jaundice (serum bilirubin >10 mg/dL) and presence of encephalopathy > stage II or massive ascites; and (7) refusal to participate.

The eligible participants continued to receive vasoconstrictor for 3 days (either terlipressin or somatostatin) and prophylactic antibiotics for 5 days (cefazolin or cefotaxime). Lactulose was administered to patients with blood or coffee-ground-like materials in the stomach. The eligible participants were randomized to two groups: the early-feeding group and the delayed-feeding group. Randomization was based on a table of random numbers in a sealed envelope. Enrollment was done immediately after endoscopic treatment was completed and variceal bleeding was arrested. Patients in the early-feeding group were asked to fast for only 4 hours following endoscopic treatment. Subsequently, a liquid diet (fruit juice, soybean juice, milk, rice in liquid form) was instituted for 3 days. Additionally, <500 cc intravenous fluid with proper electrolyte supplement per day was administered. Thereafter, a soft diet was provided for 3 days, after which a regular diet was resumed since the seventh day after endoscopic treatment. Patients in the delayed-feeding group were asked to absolutely fast for 48 hours after endoscopic treatment, and 1500 cc/day intravenous fluids (normal saline or glucose water) with proper electrolytes were administered for 2 days. After 2 days of fasting, a liquid diet was given for 1 day, and subsequently, a soft diet was given for 3 days, and then a regular diet was instituted on the seventh day after endoscopic treatment. If rebleeding occurred within 7 days of endoscopic therapy, patients in both groups were again asked to fast for 48 hours, and then put on a liquid diet for 1 day followed by a soft diet for 4 days.

The definitions of treatment failure, very early rebleeding, initial hemostasis, and 5-day hemostasis were similar to those described previously.[11]

Treatment failure was defined as failure to control acute bleeding episodes or very early rebleeding or death within 5 days. *Failure to control acute variceal bleeding* was defined as the occurrence of any of the following events within 48 hours of enrollment, based on the modified criteria of the Baveno III consensus:[11] (1) fresh hematemesis after enrollment; (2) sudden onset of reduction in blood pressure of ≥20 mmHg and/or an increase in pulse rate of ≥20 beats/minute with 2 g drop in hemoglobin; (3) transfusion of four units of blood required to increase the hematocrit to above 27% or hemoglobin to above 9 g/dL; and (4) death. *Very early rebleeding* was defined as when the criteria for failure to control acute variceal bleeding occurred between 48 hours and 120 hours after enrollment in patients achieving control of acute bleeding. *Control of acute bleeding* (initial hemostasis) was defined as when the criteria for failure did not occur within 48 hours of enrollment. A *5-day hemostasis* was defined as when the criteria for failure to control acute variceal bleeding and very early rebleeding did not occur within 5 days of enrollment. A nasogastric tube was not routinely inserted after initial endoscopy. However, a nasogastric tube was inserted in cases of failure to control

acute bleeding or episodes of very early rebleeding. Failure to control acute bleeding and very early rebleeding were assessed by two experienced clinicians. Patients with failure of initial hemostasis or very early rebleeding were treated with a vasoconstrictor, a proton pump inhibitor, and EVL or balloon tamponade as clinically indicated.

At the time of enrollment, the severity of the liver disease was classified according to Child–Pugh's classification[12] and the model-for-end-stage-liver-disease score.[13] The sizes of the esophageal varices were classified according to Beppu et al's[14] criteria. After the patients were hospitalized for more than 5 days, the surviving patients in both groups received regular EVL and beta-blockers to prevent rebleeding.[15] All the patients received abdominal ultrasound to detect the presence of ascites or liver tumor on enrollment. Newly developed ascites, infection, and hospitalization days were recorded. The detection of newly developed ascites after enrollment was performed by the use of ultrasound on clinical suspicion of ascites. Blood and frozen plasma transfusion and albumin infusion were administered to patients in both groups as clinically indicated. All the patients signed an informed consent. Our study was approved by the institution of review board at our hospital.

Emergency endoscopy was performed to detect the bleeding source if rebleeding occurred, and vasoconstrictors were administered. If ulcer bleeding was noted, a proton pump inhibitor was given for 8 weeks. The primary end points were the success rate of the initial hemostasis, very-early-rebleeding rate, and ulcer-bleeding rate. The secondary end points included the amounts of blood transfusion, new development of ascites, hospitalization days, and mortality within 42 days.

2.1. Sample-size calculation and statistical analysis

A meta-analysis showed that the hemostatic rate of endoscopic therapy alone in the control of acute variceal bleeding was 58%, and the combination of vasoconstrictor and endoscopic therapy was 77%.[3] Generally, the hemostatic rate of endoscopic treatment plus vasoconstrictor is nowadays around 80–90%.[2] The 5-day hemostatic rate may also be as low as 66%.[16] We presumed that the hemostatic rate was 90% in patients not allowed to take food for 48 hours after endoscopic treatment (delayed feeding), and 65% in individuals allowed to take food since 4 hours after endoscopic treatment (early feeding), and approximately 35 participants would be required for each group with a two-tailed test to achieve a beta value of 0.1 and an α error of 5%. The data were expressed as mean $\pm$ standard deviation. The statistical analysis was based on an intention-to-treat principle. The quantitative variables were compared according to Student t test, and the qualitative variables were compared with the Chi-square test and Fisher's exact test when appropriate. All p values were two tailed. A $p < 0.05$ was considered significant.

3. Results

A total of 133 patients were screened, and 63 patients were excluded arising from HCC (24 patients), greater than 80 years old (8 patients), chronic renal failure (7 patients), respiratory failure (2 patients), deep jaundice (4 patients), failure to arrest acute variceal bleeding (8 patients), and refusal to participate (10 patients). Finally, 70 patients were enrolled in the trial: 36 patients in the early-feeding group and 34 patients in the delayed-feeding group (Fig. 1). Both groups were comparable in baseline characteristics, such as etiologies of cirrhosis, severity of liver disease as shown by Child–Pugh's class and model-for-end-stage-liver-disease scores, severity of esophageal varices, proportion of active bleeding, the use of vasoconstrictors, and the amount of blood transfusion before endoscopic therapy (Table 1). No participants were lost to follow-up.

The main outcomes are shown in Table 2. The rubber bands applied to treat acute variceal bleeding were similar in both treatment groups. Treatment failure or failure in the control of acute bleeding was not encountered in each treatment group. In the early-feeding group, one patient rebled on the 27th day. Three patients in the delayed-feeding group rebled on 12 days, 14 days, and 27 days after endoscopic therapy, respectively. Two of these patients presented with active variceal bleeding at index endoscopy. All these patients were successfully rescued with a vasoconstrictor and repeated EVL. The proportion of patients receiving beta-blockers and the mean dose of carvedilol was similar between both groups (Table 2).

Adverse events, including ulcer bleeding in one patient, abdominal pain in one patient, bacterial infection in three patients (one with bacteremia and two patients with urinary tract infection), and fever in seven patients, were noted in the early-feeding group. In the delayed-feeding group, two patients had abdominal pain, two patients had dysphagia, two patients had bacterial infection, and six patients had fever. No significant differences existed between both treatment groups. No patients developed aspiration pneumonia.

The amount of blood transfusion was similar between both groups. On enrollment, 15 patients in the early-feeding group and 14 patients in the delayed-feeding group had ascites. Newly developed ascites were noted to occur in three patients in the early-feeding group and six patients in the delayed-feeding group ($p = 0.24$). The mean hospital stay was 6.0 ± 2.4 days (range: 2–17 days) in the early-feeding group, and 7.5 ± 3.1 days (range: 3–22 days) in the delayed-feeding group ($p < 0.05$). Two patients in the delayed-feeding group died of sepsis on 22 days and 42 days after enrollment, respectively. The survival at 6 weeks after variceal bleeding was similar between both treatment groups.

4. Discussion

Following endoscopic therapy of variceal bleeding, the issue of when to refeed these patients has rarely been investigated. This may imply that feeding is generally regarded as a negligible factor in the management of bleeding varices. On the other hand, it is usually believed that systematic fasting is required in case of patients with upper gastrointestinal bleeding.[17] The main reason of delay in feeding may be ascribed to the fear of occurrence of early rebleeding induced

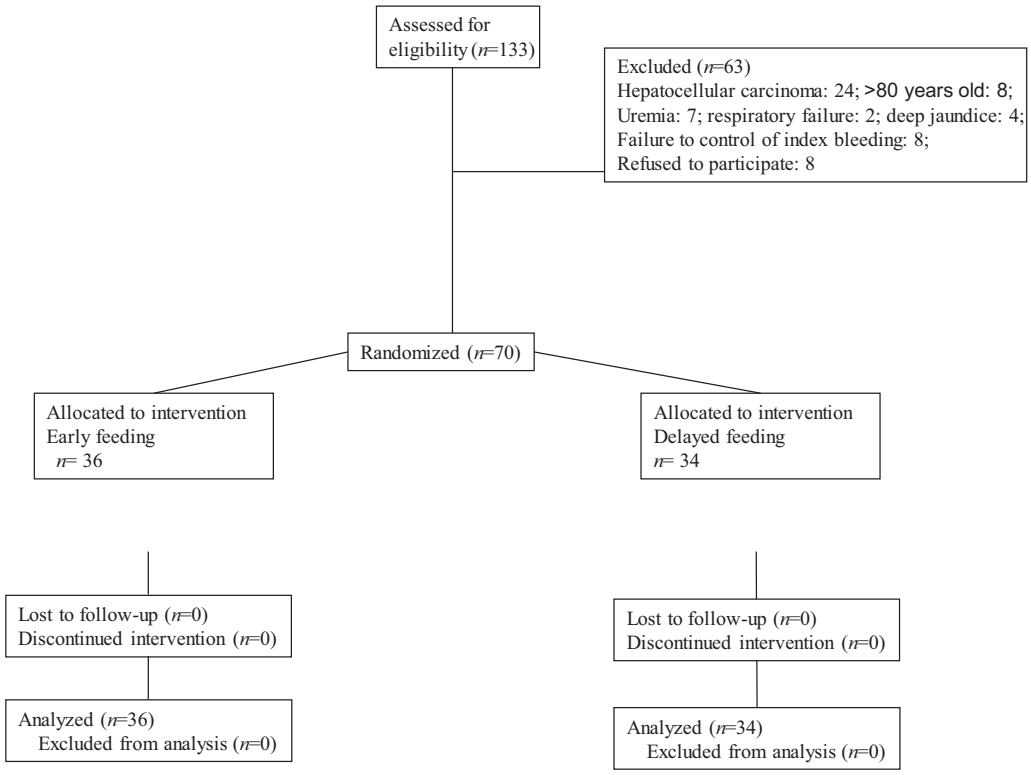

Fig. 1. A flowchart of patient allocation.

Table 1
Baseline data of both groups.

	Early-feeding group (n = 36)	Delayed-feeding group (n = 34)	p
Age (y)	47.5 ± 12.6	53.2 ± 11.8	0.60
Male/female	31/5	28/6	0.74
Etiologies			0.50
Alcohol	19	17	
HBV	7	5	
HCV	7	12	
HBV + HCV	3	0	
Albumin (g/L)	3.0 ± 0.5	3.1 ± 0.6	0.85
Bilirubin (mg/dL)	2.2 ± 1.6	2.5 ± 1.9	0.62
Prothrombin time, prolongation (s)	2.9 ± 2.2	3.1 ± 2.0	0.75
Ascites	15	14	> 0.99
Encephalopathy	1 (2%)	1 (2%)	> 0.99
Child–Pugh score	7.6 ± 1.8	8.2 ± 2.2	0.30
Child–Pugh (A/B/C)	10/14/12	11/17/6	0.55
Hemoglobin (g/dL)	8.5 ± 2.3	9.0 ± 2.3	0.66
Creatinine (mg/dL)	1.1 ± 0.3	1.1 ± 0.4	0.95
MELD score	12.4 ± 3.7	13.3 ± 4.2	0.62
Size of esophageal varices F1/F2/F3	6/22/8	5/22/7	0.90
Gastric variceal bleeding	4	3	> 0.99
Active variceal bleeding	11 (31%)	7 (21%)	0.19
Terlipressin/somatostatin	36/1	33/1	> 0.99
Presence of hepatocellular carcinoma	6 (16%)	7 (26%)	0.76
Blood transfusion (units)	3.1 ± 2.3	2.7 ± 2.2	0.50

HBV = hepatitis B virus; HCV = hepatitis C virus; MELD = model for end-stage liver disease.

by refeeding. In addition, repeated endoscopic examination and therapy may be required in patients with very early rebleeding. The decision to delay feeding is usually based on clinicians' experience or experts' opinion rather than evidence based.[17,18] That was why we performed this controlled study.

Nowadays, EVL has replaced EIS as the endoscopic therapy of choice for acute esophageal variceal bleeding.[1,4,5] Stiegmann and Goff[19] were the first to employ EVL to treat esophageal varices. They did not mention any specific restriction of feeding on patients receiving band ligation. Following the band ligation of varices, the ligated varices and tissues may evoke transient dysphagia to solid food.[4,19] The rebleeding rates associated with EVL varied greatly between studies, and rates ranging from 2% to 54% have been recorded.[1,2,20,21] Aside from other reasons, this discrepancy is very

Table 2
Main outcomes in the two treatment groups.

	Early-feeding group (n = 36)	Delayed-feeding group (n = 34)	p
Rubber bands	3.5 ± 0.5 (2–5)	3.2 ± 0.6 (3–5)	0.75
Treatment failure	0	0	> 0.99
Failure to control acute bleed	0	0	> 0.99
Very early rebleeding	0	0	> 0.99
Use of beta-blockers	8 (22%)	10 (29%)	0.49
Dose of carvedilol (mg/d)	10.9 ± 1.5	10.6 ± 1.7	0.85
Rebled between 6 d and 42 d	1 (3%)	3 (8.8%)	0.34
Hospital stay (d)	6.0 ± 2.4	7.5 ± 3.1	<0.05
Blood transfusion (units) after endoscopy	1.83 ± 1.25	2.15 ± 1.60	0.70
42-d mortality	0	2 (6%)	0.49

likely to be related to the variation in timing of refeeding after EVL. However, this factor was rarely mentioned in the methodology of these studies.

Previously, Laine et al[22] have demonstrated that immediate refeeding has similar outcomes to delayed refeeding among patients with low risk of nonvariceal bleeding. The situation of variceal bleeding is quite different from that of peptic ulcer bleeding. Hebuterne and Vanbiervliet[17] made a review on feeding of patients with upper gastrointestinal bleeding, and recommended that feeding should be delayed for at least 48 hours after endoscopic therapy because early refeeding may cause a shift in blood flow to the splanchnic circulation, which in turn could lead to an increase in pressure and an increased risk of rebleeding from the varices.

Our study included cirrhotic patients with acute variceal bleeding, both active bleeding and inactive bleeding at endoscopy. Our results revealed that early feeding with a liquid diet as early as 4 hours after endoscopic therapy did not enhance rebleeding as compared with patients with delayed feeding for 48 hours. The adoption of lagging 4 hours after EVL in the early-feeding group was anticipation for emptying of old blood in the stomach by the use of lactulose. Patients with active variceal bleeding are generally predisposed to have an appreciably high incidence of early rebleeding.[1,2,23,24] The policy of early feeding also did not have any impact on our patients presenting with active bleeding at endoscopic therapy. Our study also enrolled some patients with gastric variceal bleeding who were treated with Histoacryl injection. Similar to previous observations,[2,9,10,21,25] the current study showed that both EVL and gastric variceal obturation with Histoacryl are highly effective in the control of esophageal and gastric varices, respectively. Among 133 patients screened for enrollment, only eight patients (6%) failed in endoscopic hemostasis. After a successful endoscopic therapy, failure to control acute bleeding as well as very early rebleeding was not encountered in both early-feeding and delayed-feeding groups. We did not measure portal blood flow and portal pressure; thus, we could not know whether early feeding with a liquid diet resulted in an enhanced portal blood flow. However, no treatment failure evoked by early feeding with a liquid diet at least reflected that the impact of early feeding on portal blood flow and portal pressure did not translate to bad clinical outcomes. Only a study has evaluated enteral nutrition in cirrhotic patients with bleeding from esophageal varices, and showed that 33% of patients with early enteral nutrition rebled compared with the figure of 10% in patients fasting for 3 days.[26] Owing to a small sample size (i.e., only 22 patients were enrolled), no statistical significant difference was reached. However, they concluded that nasogastric-tube feeding may be deleterious on the short-term evolution of bleeding.[26] Based on our study, early oral feeding with a liquid diet may be instituted in patients with successful endoscopic hemostasis of either esophageal or gastric varices. However, solid food is still not encouraged in the first few days after banding ligation of varices. This is to prevent food impaction in the esophagus, as well as to guard against the occurrence of very early rebleeding. The clinical outcomes regarding rebleeding rates, mortality, and adverse events were similar in both groups. However, hospitalization days could be significantly shortened in those patients with early refeeding. The incidence of new development of ascites was slightly lower in patients with early refeeding. Possibly, a larger sample size is required to detect the difference. These findings proved that early feeding with a liquid diet was rather safe. It was demonstrated that up to 60% of decompensated cirrhotic patients were noted to have malnutrition.[27] Prolonged fasting may be detrimental to these patients. Early feeding in patients with successful endoscopic hemostasis of variceal bleeding has the advantages of increase in patients' satisfaction of desire for feeding, supply of more calories, shortening of hospital stay, and a possible decrease of ascites development. Our patients resumed a regular diet after 7 days of EVL. The safety of early resumption of a regular diet or solid foods remains to be investigated. The strengths of the current study include that this is the first randomized controlled trial to assess the impact of foods on hemostasis of variceal hemorrhage. Our study has several limitations. First, the sample size may be not enough. Up to now, there have been no available data that could be cited as a reference to estimate the required sample size. The calculation of the sample size was based on previous reports of 5-day hemostasis by a combination of EVL and vasoconstrictors (i.e., in the order of 66−100%).[4,16,20] We thus presumed that the hemostasis may be better in the delayed-feeding group and may be worst in the early-feeding group. Unexpectedly, both groups achieved 100% 5-day hemostasis. This may truly reflect that early feeding with a liquid diet does not have any bad impact on hemostasis, rather than ascribed to an inadequacy of sample size. Second, factors, such as the caloric intake, and the amount of liquid diet and solid foods, were not assessed in this trial. If an adequate caloric intake could be provided in the first few days after endoscopic therapy, this would be quite helpful for cirrhotic patients.

In conclusion, our study demonstrated that early feeding with a liquid diet in conscious patients after successful endoscopic therapy of varices can shorten the hospital days. However, we still need a larger sample size to investigate the impact between early feeding and hemostasis of variceal bleeding.

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