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Does very Early (Less than 6 Hours) Endoscopic Management Change the Outcomes of Acute Variceal Bleeding: A Retrospective Comparative Study from Southern India

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Abstract

Background: In cirrhotic patients, bleeding episodes are associated with significant mortality and morbidity.

Aim: This study aims at evaluating outcomes of very early (< 6 hours) versus later (6 - 24 hours) endoscopic therapy in patients with acute variceal bleeding.

Method: Retrospective observational cohort study done in patients who presented with acute variceal bleeding at Kasturba Medical College, Mangalore from January 2015 to December 2016. Patients were divided into group I (very early < 6 hours) and group II (later 6 - 24 hours) based on time to endoscopy. Groups were compared for outcomes including failure of initial control (upto 48 hrs), very early rebleeding (1 - 5 days), early rebleeding (5 - 30 days) and mortality upto 30 days.

Result: Out of the total 99 patients, 62 were in group I while 37 were in group II. Mean CTP (7.74 vs 7.7) and MELD (14.19 vs 13.83) scores were comparable in both groups. Overall high risk factors for rebleeding were age > 60 years (21% vs 3%: p - 0.003), creatinine > 1.4 mg/dl (37% vs 7%: p - 0.005), haemoglobin at presentation < 7 gm% (26% vs 5%: p - 0.004) and large oesophageal varices (16% vs 4%: p - 0.004). Risk factors including age > 60 years and Hb at presentation < 7 gm% were higher in group II. Very early rebleeding (1.6% vs 5.4% p - 0.286), early rebleeding (3.2% vs 13% p - 0.053) and mortality (3.2% vs 10% p - 0.126) were more cmmon in group II patients.

Conclusion: This study reveals that outcomes with very early endoscopic therapy (< 6 hours) are better than later endoscopic therapy (6 - 24 hours) in acute variceal bleeding patients.

Key words: Variceal, rebleeding, endoscopy.

Introduction

Acute variceal bleeding is the most significant cause for morbidity and mortality in patients with portal hypertension. Oesophageal varices are detected in about 50% of cirrhosis patients, and approximately 5 - 15% of cirrhosis patients' show newly formed varices or worsening of varices each year. Even in today's advanced endoscopic era, mortality with acute variceal bleeding is up to 30%[1]. Aggressive resuscitation has shown a mortality benefit in the setting of upper gastrointestinal bleeding[2].

Early endoscopic therapy is proven to be beneficial. The proposed advantages of undergoing earlier endoscopy include achieving haemostasis more quickly, possibly preventing complications, decreasing transfusions and length of hospital stay for these patients[3,4]. The American Association for Study of Liver Diseases (AASLD)[5] and BAVENO VI[6] guidelines have proposed early endoscopic therapy within 12 hours while the Asia Pacific Association for Study of Liver Disease (APASL) guideline has proposed endoscopic therapy within 6 hours in patients with acute variceal bleeding[7]. Time to endoscopy in variceal bleeding is still a matter of debate. This study aims at evaluating outcomes of very early (< 6 hours) vs later (6 - 24 hours) endoscopic therapy in patients with acute variceal bleeding. As per our knowledge, this is the first study from India comparing outcome of variceal bleed with respect to time to endoscopy.

Methodology

Our study design was a retrospective observational cohort study. This study was conducted at Kasturba Medical College, Manipal University, Mangalore. Study population included patients who presented with acute variceal bleeding and underwent endoscopic therapy. The study period was from January 2016 to December 2017. The research protocol was approved by the institutional ethics committee. Twelve patients who had probable variceal bleed and died prior to endoscopy were excluded from the study. Data was

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collected using discharge codes of the hospital. Follow-up information was obtained from the outpatient records and in few cases by telephonic contact. Demographic characteristics, clinical profile, Child Turcotte Pugh score (CTP), Model for End-stage Liver disease (MELD), endoscopic findings and outcomes were recorded. All the aetiological work-up for cirrhosis was done. On endoscopy, presence of ooze, red wale signs and/or white nipple sign from the varices were considered as source of bleed. In the absence of signs of recent haemorrhage, mere presence of gastric and/or oesophageal varices were considered as indeterminate source of bleed. All patients received pharmacological therapy including injection octreotide, intravenous antibiotics, antiemetics, crystalloids, endoscopic therapy and supportive care. For oesophageal variceal bleeding, patients underwent endoscopic variceal ligation (EVL) while for gastric varices cyanoacrylate glue was injected into varices. Danis stent was used in patients with refractory variceal bleed. Endoscopic evidence of ooze or spurting from varices were considered as active variceal bleeding. Patients were divided into group I (very early < 6 hours) and group II (later 6 - 24 hours) based on time to endoscopy.

Failure of initial control was considered in the presence of haematemesis within 48 hours of endoscopic therapy (after two hours of therapy). Very early rebleed was defined as bleeding between 48 hours - 120 hours after initial control[7]. Early rebleed was considered as bleed between 120 hours - 30 days[7]. Patients in both groups were followed-up for 30 days. Groups were compared for outcomes including failure of initial control (upto 48 hrs), very early rebleeding (2 - 5 days), early rebleeding (5 - 30 days) and mortality upto 30 days. Rebleeding patients were treated with repeat endoscopic therapies, radiological intervention, or surgical management.

Statistical analysis: Continuous data was expressed as mean ± standard deviation. Non-parametric data was expressed as percentage or exact frequencies. Comparison between categorical data was done using Chi-Square test. Comparison between continuous data was done using Student't' test. P value less than 0.05 was taken as significant. A statistical package SPSS version 17.0 was used.

Observations

Out of the total 99 patients, 62 were in the group I while 37 were in group II. Study included 77 oesophageal variceal bleed, 14 gastric variceal bleed and 8 indeterminate site of bleed. Most common aetiology of cirrhosis was alcohol followed by cryptogenic in both groups. Mean age in group I was 53 ± 11 years with 88% males while mean age in group II was 53 ± 8 years with 89% males. Mean CTP (7.74 vs 7.7) and MELD scores (14.19 vs 13.83) were comparable in both groups, although in group I patients with CTP class A were higher in number than group II as shown in Table I.

Table I: Baseline parameters in group I and II.

Parameters	Group I (%)	Group II (%)
Total patients	62 (62.6%)	37 (37.4%)
Aetiology		
Alcohol	41 (66%)	22 (59%)
Cryptogenic	19 (30%)	13 (35%)
Non cirrhotic	2 (4%)	2 (6%
Syncope	13 (20%)	9 (24%)
PR > 100/min	37 (59%)	22 (59%)
BP < 90/mmHg	8 (13%)	12 (36%)
Platelet count > 1,00,000/mm^3	41 (66%)	25 (67%)
Platelet countde 1,00,000/mm^3	21 (34%)	12 (33%)
Creatinine > 1.4 mg/dl	4 (6%)	3 (8%)
Creatinine ≤ 1.4 mg/dl	58 (94%)	34 (92%)
Mean CTP score	7.74 ± 2.3	7.7 ± 1.4
A	22 (35%)	4 (10%)
B	30 (48%)	28 (75%)
C	10 (17%)	5 (15%)
Mean MELD score	14.19 ± 2.3	13.83 ± 3.2
> 12	36 (58%)	25 (67%)
≤ 12	26 (42%)	12 (33%)
Oesophageal varices		
Small	1 (1%)	2 (5%)
Medium	31 (50%)	15 (40%)
Large	28 (45%)	15 (40%)
Gastric varices		
GOV1	7 (11%)	8 (20%)
IGV1	3 (4%)	3 (8%)
Primary therapy		
EVL	58 (93%)	31 (83%)
Glue	10 (16%)	11 (29%)
Co-morbidities		
Diabetes mellitus	20 (34%)	12 (33%)
Hypertension	16 (25%)	8 (22%)
Ischaemic heart disease	4 (6%)	–

Footnote: CTP - Child Turcotte Pugh, MELD - Model for End Stage Liver Disease, GOV1 - Gastro-oesophageal varices type 1, IGV1 - Isolated gastric varices type 1, EVL - Endoscopic Variceal Ligation.

None of the patients developed failure of initial control therapy. Overall 10 patients developed rebleed in the study upto 30 days follow-up; out of ten three were in group I

while seven were in group II. We compared patients with rebleed (10) vs patients without rebleed (89) in overall study group. Factors including age> 60 years (21% vs 3%: p - 0.003), creatinine > 1.4 mg/dl (37% vs 7%: p - 0.005), Hb at presentation < 7 gm% (26% vs 5%: p - 0.004) and large oesophageal varices (16% vs 4%: p - 0.004) were higher in patients with rebleeding and were statistically significant. These factors were considered as overall rebleeding risk factors in our study.

These overall rebleeding risk factors were compared in group I and group II. Factors including age > 60 years and haemoglobin (Hb) at presentation < 7 gm% were higher in group II and were statistically significant as shown in Table II.

Table II : Comparison of risk factors for rebleeding between two groups.

S. No.	Risk factors for rebleeding	Very early endoscopic therapy (< 6 hours)	Later endoscopic therapy (6 - 24 hours)	P value
1.	Age > 60 years	15/62 (24%)	17/37 (45%)	0.025
2.	Haemoglobin at presentation < 7 gm%	8/62 (12%)	11/37 (29%)	0.039
3	Creatinine > 1.4 mg/dl	5/62 (8%)	3/37 (8%)	0.993
4	Grade III oesophageal varices	28/62 (45%)	15/37 (40%)	0.653

Out of ten rebleed patients, eight underwent second gastroscopy. Three had post-EVL ulcer, three had oesophageal varices and two had gastric varices as culprit source of rebleed. Two patients succumbed prior to their repeat gastroscopy as shown in Fig. 1.

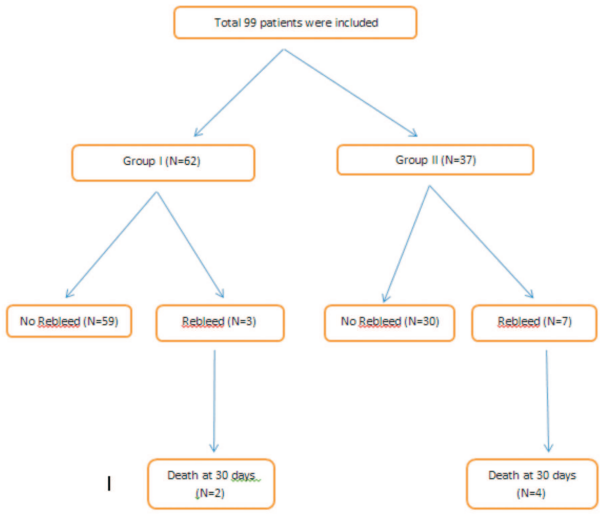

Fig. 1: *Flow chart showing the study cohort and their outcomes.*

In group I , one patient had very early rebleed while two had early rebleed. One patient with very early rebleed had large oesophageal varices with spurter. Endoscopic variceal ligation was tried but failed due to poor vision . He underwent oesophageal self expanding metallic stent placement (Danis stent) as emergency therapy. He was found to have oozing blood from varices even with SEMS in situ. He underwent direct intrahepatic porto-systemic shunt as definitive therapy and survived while two patients with early rebleed succumbed to their illness, prior to stabilisation and repeat endoscopy. In both patients suspected source of bleed was post-EVL ulcer.

In group II, two patients had very early rebleed while five patients had early rebleed . Out of the two patients with very early rebleed, one underwent balloon retrograde transvenous obliteration for gastric varices and survived while second patient had oozing from gastric varices even after second glue therapy. He had undergone repeated glue injection in past. He was subjected for surgical therapy which showed intraoperatively large ulcer (post-glue therapy) in fundus. He underwent under running of bleeding vessel at ulcer base but he died. Out of five patients with early rebleed, three succumbed to their illness. In all three patiens who succumbed, culprit cause of rebleed was post-EVL ulcer on repeat endoscopy. All three patients underwent pharmacological therapy with terlipressin infusion and were assessed for radiological and surgical intervention.

Comparing the outcomes in group I and group II we found that, very early rebleeding (1.6% vs 5.4% p - 0.286), early rebleeding (3.2% vs 13% p - 0.053) and mortality (3.2% vs 10% p - 0.126) were more in group II patients, although p values were not significant as shown in bar diagram as shown in Fig. 2. In rebleed patients who succumbed to their illness, most common cause was post-EVL ulcer (5 out of 6 patients). We concluded that Post-EVL ulcer was most difficult to treat cause of rebleed in our study.

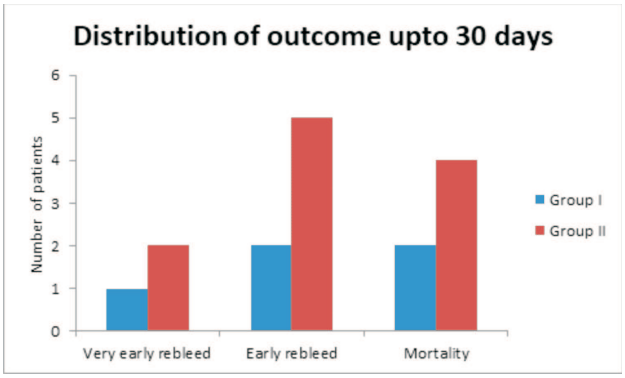

Fig. 2: *Distribution of outcome up to 30 days.*

Discussion

Portal hypertension is the most common complication of cirrhosis of liver. Variceal bleeding, a life-threatening complication of portal hypertension, leads to most of the cirrhosis-related mortalities[8]. Endoscopic therapy is the mainstay of treatment of variceal bleeding. With advancement in endoscopic technique and endoscopic therapeutic modalities, there is substantial decrease in the mortality related with variceal bleeding from 40% to 20%[9,10]. One of the unsolved issues is time to endoscopy. This study is aimed at primarily studying the impact of timing of endoscopy on rebleeding and mortality. No similar study is reported from India.

Oesophageal varices were the most common source of bleed in our study , as reported in similar studies done in the past[11]. The severity of liver disease was assessed by the Child Pugh score. Group I had more Child class A patients as compared to group II. Child class B patients were more in group II. This is explained as higher stage of liver cirrhosis is often associated with severe portal hypertension. This leads to increase in severity of variceal bleed, requiring more time for stabilisation prior to endoscopic therapy. MELD score and co-morbidities were comparable in both groups.

All the patients received pharmacological therapy alongwith appropriate endoscopy therapy. Overall rebleeding risk factors in our population were age > 60 years, Hb < 7 gm% at presentation, creatinine > 1.4 mg/dl and presence of large oesophageal varices which were reported in prior studies also. Rebleeding risk factors including age > 60 years and Hb < 7 gm% at presentation were higher group II, indicating these group of patients had more massive bleed and required more time for stabilisation prior to endoscopy, contributing for worse outcome in group II patients.

In our study, we found that very early endoscopic therapy (< 6 hours) was beneficial in reducing mortality, very early rebleeding and early rebleeding events. Early adequate control of bleeding leads to overall improvements in the outcomes. Similar results were noted in past studies. Cooper *et al*[11] compared early endoscopy to delayed endoscopy and concluded that early endoscopy was beneficial in reducing recurrent bleeding and the need for surgery. In study done by Sarin *et al*[12] there was no significant difference between early and late endoscopy in terms of mortality, need for surgery or transfusion requirements; however, their study population was not restricted to variceal bleeding. Wysocki *et al*[13] showed that in patients with acute variceal bleeding who were subjected for late endoscopy mortality increased from 8.25% to 15.3% . Cheung *et al*[14] evaluated the outcomes of acute variceal bleeding patients with time to endoscopy in three different groups (< or = vs > 4 h, < or = vs > 8 h, and < or = vs > 12 h). He did not find significant difference in three groups.

In our study post-EVL ulcer bleeding was seen in 5% of the patients. It was the most common source of rebleed in our study. This can be explained by the fact that most common source of primary bleed was oesophageal variceal bleed in our study. In literature incidence post-EVL bleed was reported as 3.5% - 15%[15] and the mortality is reported to be as 52%[16]. Mortality in post-EVL group rebleed was 83% in our study. We concluded that Post-EVL ulcer group rebleed is difficult to treat.

Conclusion

To conclude, our study showed that time to endoscopy affects the outcome in patients with variceal bleeding. Early endoscopy therapy (< 6 hours from presentation to the hospital), significantly reduces the incidence of early rebleeding and though not significant, improves the outcome with respect to very early rebleeding, and mortality. To confirm these findings large scale, multicenter, prospective study is required.

Limitation of study

Limitation of our study was that we divided patients in two groups on the basis of time to endoscopy from the time of presentation in hospital. The time between the onset of bleeding and presentation to the hospital was not considered in the study. Being retrospective study, selection bias was included. We have not measured hepatic venous pressure gradient (HVPG) as indirect measure of portal pressure. Confounding factors including time of presentation to hospital (day/night/holiday), availability of endoscopist and availability of blood products were not evaluated in our study. Sample size was low.

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