

The International Normalized Ratio does not Reflect Bleeding Risk in Esophageal Variceal Hemorrhage

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ABSTRACT

Background/Aims: The international normalized ratio (INR) has not been validated as a predictor of bleeding risk in cirrhotics. The aim of this study was to determine whether elevation in the INR correlated with risk of esophageal variceal hemorrhage and whether correction of the INR prior to endoscopic therapy affects failure to control bleeding. **Patients and Methods:** Patient records were retrospectively reviewed from January 1, 2000 to December 31, 2010. Cases were cirrhotics admitted to the hospital due to bleeding esophageal varices. Controls were cirrhotics with a history of non-bleeding esophageal varices admitted with ascites or encephalopathy. All variceal bleeders were treated with octreotide, antibiotics, and band ligation. Failure to control bleeding was defined according to the Baveno V criteria. **Results:** We analyzed 74 cases and 74 controls. The mean INR at presentation was lower in those with bleeding varices compared to non-bleeders (1.61 vs 1.74, $P = 0.03$). Those with bleeding varices had higher serum sodium (136.1 vs 133.8, $P = 0.02$), lower hemoglobin (9.59 vs 11.0, $P < 0.001$), and lower total bilirubin (2.47 vs 5.50, $P < 0.001$). Multivariable logistic regression showed total bilirubin to inversely correlate with bleeding (OR = 0.74). Bleeders received a mean of 1.14 units of fresh frozen plasma (FFP) prior to endoscopy (range 0-11 units). Of the 14 patients (20%) with failure to control bleeding, median INR (1.8 vs 1.5, $P = 0.02$) and median units of FFP transfused (2 vs 0, $P = 0.01$) were higher than those with hemostasis after the initial endoscopy. **Conclusions:** The INR reflects liver dysfunction, not bleeding risk. Correction of INR with FFP has little effect on hemostasis.

Key Words: Coagulopathy, fresh frozen plasma, portal hypertension

Received: 24.10.2014, Accepted: 23.12.2014

How to cite this article: Hshieh TT, Kaung A, Hussain S, Curry MP, Sundaram V. The international normalized ratio does not reflect bleeding risk in esophageal variceal hemorrhage. Saudi J Gastroenterol 2015;21:254-8.

In patients with liver cirrhosis, hemorrhage of esophageal varices remains a serious complication, despite advances in medical and endoscopic technology, with an estimated mortality of 15%–20%.^[1-3] In the setting of variceal bleeding, common clinical practice is to address the perceived coagulopathy associated with an elevated International Normalized Ratio (INR), through correction with fresh frozen plasma, in an attempt to control the bleeding. Current recommendations from the American Association for the Study of Liver Diseases (AASLD) regarding management of bleeding esophageal varices incorporates the use of fresh frozen plasma (FFP) to correct the International Normalized Ratio (INR), stating “The transfusion of fresh frozen plasma and platelets can be

considered in patients with significant coagulopathy and/or thrombocytopenia.”^[4] However, the INR, which was initially developed to measure anticoagulation in patients taking warfarin, has not been validated in clinical studies as a measure of bleeding risk. In fact, evidence suggests that INR is likely an inaccurate measure of coagulopathy in liver disease due to the complexity and dynamic nature of coagulation in cirrhosis.^[5-8] Therefore, correction of the INR may not be beneficial in the management of bleeding esophageal varices.

The aims of this study were to examine whether elevation in the INR increases risk of bleeding from esophageal varices and to determine whether transfusion of FFP to correct the INR in the setting of variceal hemorrhage reduced the incidence of failure to control bleeding.

PATIENTS AND METHODS

Case selection and study design

Patients were selected by review of all admissions to Beth Israel Deaconess Medical Center (BIDMC) from

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	DOI: 10.4103/1319-3767.161646

the emergency room over a 10-year period of time, from January 1, 2000, to December 31, 2010. The data collection protocol was designed before case selection. All patient cases included in this study were selected based on an international classification of diseases-9 (ICD-9) code of cirrhosis, which was confirmed by liver biopsy, radiologic imaging, or clinical evidence of liver decompensation. Exclusion criteria were the presence of transjugular intrahepatic portosystemic shunt (TIPS), use of warfarin, and diagnosis of an underlying coagulation disorder such as hemophilia. In addition, because admission data from outside hospital transfers was unreliable, patients transferred from other facilities were also excluded.

A case-control design was utilized, defining cases as those with liver cirrhosis admitted for esophageal variceal bleeding. After selection of our cases, we then selected an equal number of controls, who were defined as patients with liver cirrhosis and esophageal varices without prior history of variceal hemorrhage, who were admitted for liver decompensation, specifically ascites or hepatic encephalopathy. The controls were matched to our cases for age, gender, use of beta-blockers, and presence of portal vein thrombosis. Presence of varices was confirmed in all patients by review of an endoscopy report performed at BIDMC, either during hospitalization for variceal bleeders or within one year prior to hospitalization for controls.

All patients with variceal hemorrhage were treated with administration of octreotide and antibiotics, followed by endoscopic variceal band ligation. Data collected included patient demographics, admission laboratory data, endoscopic findings, use of beta-blockers, use of aspirin, and presence of portal vein thrombosis. For variceal bleeders, we also recorded the number of units of FFP transfused and INR after FFP transfusions.

A sample size calculation was performed, powering as a noninferiority study. The alternative hypothesis was that the INR among bleeders is statistically similar to that of nonbleeders, whereas the null hypothesis was that the INR among bleeders is higher than nonbleeders. Using an alpha of 0.05, power of 80%, standard deviation of the INR of 0.4, and a noninferiority limit of 0.2, it was calculated that 69 patients would need to be in each group, for a total of 148 patients. In total, 74 total patients were identified as study subjects and an equal number of controls were randomly selected.

Failure to control bleeding

The patients with variceal hemorrhage were further classified into those with and without failure to control bleeding, according to the Baveno V consensus criteria.^[9] Failure

to control bleeding is defined as death or need to change therapy defined by one of the following criteria:

- Fresh hematemesis or NG aspiration of 100 mL of fresh blood 2 h after the start of a specific drug treatment or therapeutic endoscopy
- Development of hypovolemic shock
- Three grams drop in hemoglobin within any 24-h period if no transfusion is administered.

Statistical analysis

Statistical analysis was performed using Stata version 10 software. Categorical variables were compared using Chi-squared analysis. Continuous variables were compared using Student's *t*-test for parametric analysis and Mann-Whitney *U* test for nonparametric analysis. Multivariable logistic regression analysis was used with variceal hemorrhage as the primary outcome. All statistical comparisons were two tailed, with a *P* value of < 0.05 required for statistical significance.

This study was approved by the Institutional Review Board at Beth Israel Deaconess Medical Center.

RESULTS

Study population characteristics

Review of medical records yielded a total of 74 patients admitted from the emergency room with a diagnosis of esophageal variceal hemorrhage. An equal number of controls were randomly selected, among review of patients admitted to our emergency room. Among the 74 control patients, 50 were admitted with ascites whereas 24 were admitted with hepatic encephalopathy. There were no significant differences between the two patient groups regarding age, gender, ethnicity, etiology of cirrhosis, use of beta-blockers, use of aspirin, or presence of portal vein thrombosis. Further details regarding study population characteristics are outlined in Table 1.

Laboratory values and risk for variceal hemorrhage

Depicted in Table 2 are mean admission laboratory values, compared between cases and controls, using Student's *t*-test. The mean admission INR level for patients with variceal bleeding was 1.61, which was significantly lower than the mean INR level of 1.74 for control patients. In addition, the bilirubin level was significantly lower among bleeders than among nonbleeders (2.46 vs 5.50, *P* < 0.001). The model for end-stage liver disease (MELD) score was also significantly higher in the nonbleeding patients, although this is related to the higher bilirubin and INR levels among this group. There were no significant differences between the two patient groups regarding sodium, creatinine, alanine aminotransferase (ALT), platelet level, and albumin.

A multivariable logistic regression model was then constructed, predicting the occurrence of esophageal variceal hemorrhage. The INR was found not to be predictive of variceal bleeding. In our model, the only independent variable that had statistical significance was bilirubin, which was found to be negatively predictive of variceal hemorrhage (odds ratio = 0.74, 95% confidence interval 0.61–0.90).

Failure to control bleeding

Among the 74 patients admitted with variceal bleeding, 14 of the patients were classified as having failure to control bleeding after endoscopic band ligation, according to the Baveno V consensus criteria. Of these 14 patients, 8 developed a three grams drop in hemoglobin, 5 developed hematemesis, and 1 developed hypovolemic shock. When comparing the median INR levels between those with and without, the median INR level was higher in those with failure to control bleeding (1.8 vs 1.5, $P = 0.02$). In addition, those with failure to control bleeding had a greater median number of FFP units transfused (2 vs 0, $P = 0.01$). Mann–Whitney U test was utilized to compare INR level and FFP transfusion between the two groups, because these variables were not normally distributed in these two patient

groups. We also evaluated the percent change in INR level between admission and after FFP transfusion, and found that FFP did not change the INR level in patients with or without failure to control bleeding [Tables 3 and 4].

DISCUSSION

The INR may be elevated in cirrhotics due to reduced synthesis of vitamin K-dependent clotting factors. However, cirrhosis is also characterized by alterations in platelet function and adhesion, hyperfibrinolysis, and reduction in anticoagulant factors such as protein C and S, all of which are unaccounted for by the INR.^[5-8,10-12] Despite lack of evidence that the INR accurately measures bleeding risk in chronic liver disease, conventional thinking in the medical community remains that elevation in the INR predisposes to bleeding. For instance, a recent study by Shah *et al.*, which surveyed the incidence of bleeding and use of blood products at a single center, found that although cirrhotics accounted for 7.7% of bleeding episodes, they consumed 32.4% of plasma administered.^[13] Another retrospective study from a single center found that liver disease, even without clinical bleeding, accounted for one of the largest

Table 1: Characteristics of the study population

Characteristics	Bleeder (n=74)	Nonbleeder (n=74)	P
Age±SD (year)	53.8±11.1	53.5±9.6	NS
Male (%)	55 (75.1)	53 (72.8)	NS
White (%)	56 (75.7)	54 (73.6)	NS
Etiology of cirrhosis: (%)			
Alcohol	32 (43.3)	34 (45.9)	NS
Hepatitis C	22 (29.7)	24 (32.4)	NS
Other	20 (27.0)	16 (21.6)	NS
Portal vein thrombosis	9 (12.2)	6 (8.1)	NS
Beta-blockers	32 (43.2)	33 (44.5)	NS
Aspirin	5 (6.7)	2 (2.7)	NS
Admission diagnosis:			
Ascites		50	
Hepatic encephalopathy		24	

Table 2: Laboratory characteristics of case and control populations on presentation to the emergency room

Characteristics	Bleeder (n=74)	Nonbleeder (n=74)	P
Sodium	136.1±5.4	133.8±5.4	NS
Creatinine	1.1±0.8	1.3±1.7	NS
Alanine aminotransferase	52.3±57.4	52.7±58.9	NS
International normalized ratio	1.61±0.3	1.74±0.4	0.04
Platelets	121.2±72.5	119.8±95.4	NS
Bilirubin	2.46±2.4	5.50±6.9	>0.001
Albumin	3.00±0.6	2.86±0.5	NS
Model for end-stage liver disease score	13.4±5.9	16.9±7.7	0.002

Table 3: Multivariable logistic regression analysis predicting outcome of variceal bleeding

	Odds ratio	P	95% CI
International normalized ratio	1.61	0.447	0.47-5.52
Bilirubin	0.74	0.003	0.61-0.90
Beta-blocker	0.94	0.880	0.45-1.96
Aspirin	8.12	0.076	0.80-82.2
Portal vein thrombosis	2.09	0.270	0.56-7.79
Platelets	0.99	0.307	0.99-1.00

Table 4: Transfusion data regarding patients with variceal hemorrhage, grouped into failure and nonfailure to control bleeding

	Failure (n=14)	Nonfailure (n=60)	P
Criteria met:			
Hemoglobin drop >3 g	8		
Hematemesis	5		
Hypovolemic shock	1		
INR (median, range)	1.8 (1.3-2.3)	1.5 (1.1-2.4)	0.03
Hemoglobin (median, range)	9.5 (7.6-12.2)	9.9 (3.5-16)	NS
Platelets (median, range)	125 (25-266)	184 (29-336)	NS
FFP transfused (median, range)	2, (0-6)	0 (0-11)	0.04
% change in INR	0	0	
PRBC transfused (median, range)	5 (0-10)	1.5 (0-8)	NS
Platelets transfused (median, range)	0 (0-3)	0 (0-2)	NS

INR: International normalized ratio, PRBC: Packed red blood cells, FFP: Fresh frozen plasma

uses of FFP transfusion.^[14] Unfortunately, due to the lack of clinical studies, professional society guidelines have not yet made recommendations against correction of the INR in the management of variceal bleeding. For instance, current AASLD practice guidelines for variceal hemorrhage state that correction of the INR with FFP transfusion can be considered in the setting of variceal hemorrhage.^[4] Additionally, the report from the Baveno V consensus workshop states that recommendations cannot be made regarding management of coagulopathy based on currently available evidence.^[9]

Our findings suggest that the INR is not an accurate indicator of variceal bleeding risk. What is unique about our study is that it is the first to directly compare INR levels between two similar groups of patients with cirrhosis and portal hypertension, who were matched for factors affecting bleeding risk such as portal vein thrombosis, aspirin use, and beta-blocker use and to show a significantly lower INR level in variceal bleeders. Furthermore, we demonstrate that patients with failure to control bleeding received more FFP, indicating the lack of utility of FFP in this situation. There have been prior studies with findings consistent with those of our study. Bosch *et al.* examined the use of recombinant Factor VII to correct prothrombin time in variceal bleeders and found no effect on failure to control bleeding.^[15] Vieira Da Rocha *et al.* explored the use of INR and other tests of coagulation in predicting bleeding from ulcers after variceal band ligation and demonstrated no difference in ulcer bleeding between patients with an INR >1.5 and those with an INR ≤1.5.^[16] However, ours is the first study to date to examine the INR specifically in the setting of variceal bleeding and to assess the effect of FFP transfusion, which is the most commonly used method to correct the INR.^[17]

The INR is an accurate measure of liver synthetic function and has been well validated as a means of indicating liver decompensation and predicting mortality in the cirrhotic patient.^[18] This likely explains why the INR was significantly higher in the cohort of nonbleeders, who likely had a greater degree of liver dysfunction. The serum bilirubin level was also higher in the nonbleeders, corroborating the notion that these patients had a greater degree of liver decompensation. There was also a trend toward a lower albumin level in the nonbleeding patients; although this was not significant, it further indicates that the nonbleeders had greater liver dysfunction.

In our analysis of variceal bleeders, we did find the median admission INR level to be higher among those patients with failure to control bleeding. We do not believe, however, that the higher INR level indicates a greater tendency to bleed, but instead reflects poorer liver synthetic function. We also think it is more likely that the transfusion of products including FFP, red blood cells, and platelets, may have led to

difficulty in controlling bleeding, through a transient increase in portal hypertension. A recent study by Villanueva *et al.* demonstrated that in cirrhotics with variceal hemorrhage, further bleeding after endoscopy occurred in those receiving more units of red blood cells. Furthermore, transfusion of red blood cells correlated with an increase in hepatic venous pressure gradient.^[19] Other studies in both humans and animals have corroborated the notion that transfusion leads to a rise in portal pressure.^[20,21] We additionally found that FFP transfusion does not appear to change the INR level in patients with acute variceal bleeds. This was consistent with findings from a prior study, which demonstrated that only 10%–12.5% of cirrhotic patients had correction of prothrombin time from FFP administration.^[22]

Transfusion of FFP is not without risks, such as allergic and anaphylactic reactions, transfusion-associated lung injury, and volume overload. Transfusion-related lung injury is the most common respiratory illness found among critical care patients and 12 times more likely in patients transfused with FFP.^[23] Allergic reactions can occur in 1%–3% of patients receiving transfusion and anaphylactic reactions, though rare, are more commonly associated with transfusion of FFP, as compared with blood transfusion.^[24] Although it is reassuring that in our study population there were no complications associated with FFP transfusion, one needs to recognize that these complications can occur and have considerable repercussions.

We acknowledge that the weakness of our study is primarily due to its retrospective study design, since patient records may have inaccuracies or missing information. For instance, Child–Pugh score could not be calculated since certain components of the score, such as severity of ascites and encephalopathy are subjective in nature. This may be of importance since studies have demonstrated Child C patients to be at higher risk of bleeding.^[16,25,26] We did however compare MELD score between the two patient groups, as a means of measuring liver dysfunction. Ultimately, it was not possible to match the patients for MELD scores without inherently matching for INR, but this factor was controlled for in the logistic regression in order to address the phenomenon of nonbleeders having statistically significant higher MELD scores.

We also acknowledge that ideally hepatic venous pressure gradient measurements should have been collected in our patients. However, this is not part of routine care at our center and therefore this data was not available for inclusion in the study. We did collect information regarding the grade of varices in each patient, by reviewing each patient's endoscopy report. However, we did not include this information in our analysis as the grade of varices is determined subjectively, depending on the opinion of the endoscopist. Due to the

retrospective nature of the study, we did not have the actual images available for review in a blinded manner to assess the grade of varices. In addition, the small number of patients meeting the criteria for failure to control bleeding limited our analyses, as we could only perform nonparametric analysis to compare those with and without failure to control bleeding.

Despite the retrospective nature of the study, we tried to minimize the study limitations by collecting data on objective variables, which are available in our medical records system. Furthermore, by only including patients admitted from our emergency room, we ensured that we had all the available data during each patient's entire hospitalization, including laboratory studies, products transfused, and the patient's clinical course. However, we acknowledge that the ideal study would be a multicenter trial, where patients with variceal bleeding are randomized to receive FFP or placebo. Our hope is that the findings from this study will help to form a basis to initiate such studies.

In conclusion, this study is the first to evaluate the relationship between INR and esophageal bleeding risk in cirrhotics. We found the mean admission INR level to be lower among variceal bleeders than among nonbleeders, indicating that the INR is not predictive of bleeding tendency in this setting. Furthermore, the INR does not significantly change in response to FFP transfusion, and transfusion of products such as FFP may in fact lead to failure to control bleeding. These findings suggest that the INR more likely reflects liver dysfunction than bleeding risk and that correction of INR with FFP has minimal impact on hemostasis. Further studies should be done to investigate this important issue.

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Source of Support: The authors declare no conflicts of interest. No grants or other financial assistance was used to support the research for this paper, **Conflict of Interest:** None declared.