Brief communication

Platelet count in predicting bleeding complication after elective endoscopy in children with portal hypertension and thrombocytopenia

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Background: Thrombocytopenia is a frequent and challenging clinical disorder in patients with portal hypertension. It can increase the risk of bleeding associated with invasive procedures. Standard treatment for thrombocytopenia usually consists of platelet transfusions, which may cause transfusion-related complications including viral or bacterial infection, allo-immunization and febrile non-hemolytic reactions. Uncertainty still exists as to the platelet level at which transfusion is indicated in conjunction with invasive procedures such as endoscopy.

Objective: To determine the predictive value of platelet level for post elective endoscopy bleeding in children with portal hypertension and thrombocytopenia.

Patients and methods: Children with portal hypertension and thrombocytopenia (platelet count <100,000 per μL) were enrolled. Those who had active gastrointestinal (GI) bleeding at the time of admission were excluded. All patients underwent elective upper GI endoscopy for esophagogastric varices surveillance and tested for complete blood count.

Results: There were 41 children (male:female = 20:21) with portal hypertension enrolled in this study. Age ranged from 2-16 years (mean±SD = 8.42±4.32 years). The etiology of portal hypertension was biliary atresia in 19 and extra-hepatic portal vein obstruction in 22. Thirty of 41 experienced previous upper GI bleeding. Endoscopic finding was 32 esophageal varices (EVs), two EVs plus gastric varices, and seven without varices. Twenty-one patients underwent endoscopy without therapeutic procedure and 20 went through endoscopic variceal ligation. Two patients developed GI bleeding post endoscopy. Platelet count of children with and without post endoscopy bleeding was not significantly different (68,500±40,305 vs. 73,025±24,030/μL, respectively; p=0.8). By applying receiver operating characteristic (ROC) curves, a platelet count cut-off value of 41,500/μL was obtained, which gave positive and negative predictive values of 12.5% and 96.9%, respectively. The accuracy of this cut-off value as evaluated by applying ROC curves was 80.5%.

Conclusion: Patients with platelet count of more than 40,000/μL were almost certainly safe to undergo elective endoscopy without prophylactic platelet transfusions and hence minimize the cost and complications of transfusion.

Keywords: Endoscopy, platelet count, portal hypertension, thrombocytopenia.
growth factor that leads to proliferation and differentiation of megakaryocytes and platelet formation [2]. Patients with chronic liver disease may have reduced TPO production that can contribute to development of thrombocytopenia. Furthermore, chronic liver diseases may be associated with coagulation abnormalities such as decreased synthesis of clotting and inhibitor factors, decreased clearance of activated factors, platelet function defects, increased platelet destruction mediated by immune mechanisms involving anti-platelet autoantibodies and platelet-associated immune complexes, hyperfibrinolysis, and accelerated intravascular coagulation [3-6]. In addition, patients with cirrhosis had reduced thrombin generation [3]. Thrombin generation correlated with platelet numbers and hence severe thrombocytopenia may limit thrombin generation in patients with cirrhosis. The bleeding tendency accounts for increased risk of morbidity and mortality in patients with liver disease undergoing diagnostic or therapeutic invasive procedures.

Endoscopy is a standard diagnostic screening tool for esophagogastric varices in patients with portal hypertension. Current guidelines recommend screening all cirrhotic patients by endoscopy to estimate the risk of bleeding [7]. After screening endoscopy, patients with medium or large varices should be treated to prevent bleeding, while all other patients should undergo periodic surveillance endoscopy.

Thrombocytopenia is a common and challenging clinical disorder in patients with portal hypertension. It can increase the risk of bleeding associated with invasive procedures. Standard therapy for thrombocytopenia typically consists of platelet transfusions, which may cause transfusion-related complications including viral or bacterial infection, allo-immunization, and febrile non-hemolytic reactions, which may occur in up to 30% of patients undergoing platelet transfusions [2].

Thrombocytopenia and its treatment can have a negative impact on outcomes and cost of therapy; costs associated with platelet transfusion can constitute a significant portion of the hospital budget. Routine diagnostic or therapeutic procedures can be complicated, prolonged, or precluded because of severe thrombocytopenia. It justifies prophylactic platelet transfusion in patients with low platelet counts before undergoing surgery or invasive procedures. Nevertheless, periodic platelet transfusion shortages can also present problems regionally particularly in rural area.

Uncertainty still exists as to the platelet level at which transfusion is indicated in conjunction with invasive procedures such as endoscopy. The present study was undertaken to determine the predictive value of platelet level for post elective endoscopy bleeding in portal hypertensive children without prophylactic platelet transfusions.

**Methods**

Children with portal hypertension and thrombocytopenia (platelet count ≤100,000/μL) who attended the liver clinic at King Chulalongkorn Memorial Hospital were enrolled. Those who had active gastrointestinal (GI) bleeding at the time of admission were excluded. All patients underwent elective upper endoscopy for esophagogastric varices surveillance and tested for complete blood count. Post endoscopy bleeding was defined by upper GI bleeding occurred within 24 hours after endoscopy.

The protocol was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University. The study’s objective was explained to participants’ guardians and their informed consents were obtained.

**Statistical analysis**

The results were expressed as the mean±standard deviation (SD). Continuous variables were tested for statistical significance with Student t-test. Determination of a platelet count cut-off value to predict post endoscopy bleeding was obtained by applying receiver operating characteristic (ROC) curves. A-p-value of <0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 13 software (SPSS Inc., Chicago, USA).

**Results**

There were 41 children (male: female = 20:21) with portal hypertension enrolled in this study. Age ranged from 2-16 years (mean±SD = 8.42±4.32 years). Platelet count ranged from 34,000-100,000/μL (72,804±24,293/μL). The etiology of portal hypertension was biliary atresia in 19 and extra-hepatic portal vein obstruction in 22. Thirty of 41 experienced previous upper GI bleeding. Endoscopic finding was 32 esophageal varices (EVs), two EVs plus gastric varices, and seven without varices. Twenty-one patients underwent endoscopy without therapeutic
procedure and 20 went through endoscopic variceal ligation. Two patients developed GI bleeding post endoscopy which were treated with platelet transfusion in one patient and packed red cell transfusion in the other one. Platelet count of children with and without post endoscopy bleeding was not significantly different (68,500±40,305 vs. 73,025 ±24,030/μL, respectively; p=0.8). By applying ROC curves, a platelet count cut-off value of 41,500/μL was obtained, which gave positive and negative predictive values of 12.5% and 96.9%, respectively. The accuracy of this cut-off value as evaluated by applying ROC curves was 80.5%.

Discussion

Thrombocytopenia remains a significant clinical problem in which platelet transfusion is the only available treatment for the management of acute bleeding. It is estimated that in the United States, around eight million units of platelets per year are transfused to diminish the risk of severe bleeding [2]. Patients with portal hypertension who are suffering from severe thrombocytopenia may require longer hospitalizations because of prophylactic platelet transfusions or because of bleeding complications. They possibly will experience significant treatment costs, additional staffing and hospital charges, and delay in planned medical procedures. Those who require multiple platelet transfusions can experience transfusion-associated complications.

Plevris et al. [8] studied in patients with primary biliary cirrhosis and reported that platelet count below 200,000/μL was strongly associated with variceal bleeding and therefore the platelet count can be used as a predictor of variceal bleeding. Controversies surround platelet transfusion practices. These include the suitable platelet dose and the threshold at which prophylactic platelet transfusions will be most effective. For uncomplicated patients (without liver disease) with platelet counts >20,000/μL, platelet transfusion is generally not required [9]. Studies now have convincingly demonstrated that a 10,000/μL threshold for prophylactic platelet transfusion is safe and effective in uncomplicated thrombocytopenic patients [10, 11].

Guidelines for platelet transfusion have been issued by several groups [12, 13]. The actual cut-off value has varied in the published literature according to the patient population and the perceived risk of the planned procedure. Some studies have found no increase in the risk of bleeding in cirrhotic patients with platelet counts above 50,000/μL undergoing invasive procedures such as liver biopsy, endoscopy, paracentesis, and liver transplantation [13-17]. None of patients in this study had concomitant coagulopathy (international normalized ratio <1.5; data not shown), therefore we did not give either prophylactic platelet transfusion or fresh frozen plasma. This study suggested that portal hypertensive patients with platelet count of more than 40,000/μL are almost certainly safe to undergo elective endoscopy without prophylactic platelet transfusions. Nevertheless, this figure of platelet level might not be appropriate in patients with cirrhosis. Since chronic liver diseases are invariably associated with coagulation abnormalities such as decreased synthesis of clotting and inhibitor factors, decreased clearance of activated factors, quantitative and qualitative platelet defects, hyperfibrinolysis, and accelerated intravascular coagulation [4]. In particular in patients with sepsis because there is evidence showing that sepsis further impairs hemostasis in patients with liver cirrhosis bleeding from esophageal varices [4]. It is not always possible to predict which patients will develop severe thrombocytopenia during undergoing invasive procedures. Because of the lack of formal guidelines for patients with chronic liver disease and the increased risk of bleeding with concomitant coagulopathy in this population, all chronic liver disease patients could potentially benefit from therapies that would increase platelet levels to >100,000/μL [18].

In this study, we did not explore the cause of extrahepatic portal vein obstruction (EPVO). However, the etiology of EPVO in children usually remains unknown [19]. Although thrombocytopenia in EPVO is caused by splenic sequestration, GI bleeding is usually controlled with endoscopic therapeutic procedures in most patients. Surgery such as portosystemic shunt and splenectomy is reserved only in patients with uncontrolled GI bleeding despite endoscopic procedures. Other methods used to treat severe thrombocytopenia include splenic artery embolization and transjugular portosystemic shunt (TIPS). These modalities carry significant cost, risk of complications, and uncertain long-term benefit thus, the use of these approaches is limited in children.

While advances have been made in platelet collection, storage, and transfusion, patients are still at risk for transfusion-related complications. Transfusion does not always ensure maintenance of
hemostatic platelet levels [12]. New therapeutic options are needed to increase safely platelet counts prior to invasive medical procedures. In the future, novel therapies for thrombocytopenia including recombinant human thrombopoietin (rHuTPO), recombinant human megakaryocyte growth and development factor (rHuMGDF), non-peptide and non-immunogenic peptide TPO mimetic (eltrombopag and AMG 531) may provide an effective alternative to transfusions, reducing the cost of therapy while increasing patient’s quality of life [18, 20]. In the meantime, standardized evidence-based guidelines for transfusion support in thrombocytopenic patients with chronic liver disease or portal hypertension during invasive procedures including liver biopsy, endoscopy, and dental extractions might be useful to the clinician. Providing clinicians with guidelines specific for this patient population may lead to cost savings and improved patient management.

In conclusion, portal hypertensive patients with platelet count of more than 40,000/μL are most likely safe to undergo elective endoscopy without prophylactic platelet transfusions and hence minimize the cost and complications of transfusion.

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References