The Effect of Transjugular Intrahepatic Portosystemic Shunt on Platelet Counts in Patients With Liver Cirrhosis

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Abstract: Thrombocytopenia is a well-known complication of liver cirrhosis. Although the pathogenesis of thrombocytopenia is not well understood, splenic congestion resulting from portal hypertension is considered the most significant underlying mechanism. Therapeutic measures that lower portal hypertension, such as transjugular intrahepatic portosystemic shunt (TIPS), are expected to improve thrombocytopenia associated with liver cirrhosis. At present, there are few studies on the effect of TIPS on platelet counts, and the results are conflicting. This article assesses the effect of TIPS on thrombocytopenia associated with liver cirrhosis. **Methods:** Seventy-four patients with liver cirrhosis who were referred for TIPS were included in this study. Platelet counts were measured on 3 different occasions over a 3-month period prior to and following placement of TIPS. Thrombocytopenia was defined as a platelet count of 150,000/mm^3 or less. Moderate thrombocytopenia was defined as a platelet count of 100,000/mm^3 or less. Severe thrombocytopenia was defined as a platelet count of 50,000/mm^3 or less. A significant increase in platelet count was defined as a 20% or higher increase from pre-TIPS values. The portosystemic pressure gradient (PSPG) was measured before and after placement of TIPS. The patency of the shunt was checked using Doppler ultrasound 24 hours and 3 months after the procedure. **Results:** Thirty-four of the 74 patients (46%) who underwent TIPS showed a significant increase in platelet count, with an average increase of 22% ($P<.0005$). Twenty-five of 40 patients (62%) with moderate thrombocytopenia showed a significant increase in platelet count, with an average increase of 36% ($P<.0005$). Patients with severe thrombocytopenia showed the greatest response to TIPS; 8 of 11 patients (73%) had a significant increase in platelet count (average increase, 55%; $P<.0005$). No correlation was found between the response to TIPS and age, sex, etiology of liver disease, pre-TIPS PSPG, or the amount of decrease in PSPG. **Conclusion:** TIPS may improve thrombocytopenia associated with liver cirrhosis. Patients with severe thrombocytopenia are more likely to benefit from this procedure. No factors other than pre-TIPS platelet count were found to influence the response to TIPS.

Thrombocytopenia is a well-known complication of liver cirrhosis.[1,2] Its incidence in patients with liver cirrhosis varies from 15% to 75% depending upon the population studied and the definition of thrombocytopenia used.[2-5] The pathogenesis of thrombocytopenia in liver cirrhosis is not well understood. Several mechanisms have been proposed, including splenic sequestration (hypersplenism),[6] platelet antibodies,[7] chronic low-grade disseminated intravascular coagulopathy,[8] absence of humoral hepatic factor,[9] alcohol toxicity,[10] and folate deficiency.[10] Splenic congestion as a consequence of portal hypertension with pooling and increased destruction of platelets within an enlarged spleen is considered the most significant cause of thrombocytopenia in patients with liver cirrhosis.[6,7] Based on this theory, therapeutic measures that lower splenic venous pressure are expected to result in at least some improvement in thrombocytopenia. However, studies with surgical shunts have yielded conflicting results; although several uncontrolled trials reported improvement in thrombocytopenia after portacaval or distal splenorenal shunts,[11-14] these favorable results could not be consistently reproduced.[1,2,15,16] Following orthotopic liver transplantation, a complete resolution of preexisting thrombocytopenia has been reported.[17]

Transjugular intrahepatic portosystemic shunt (TIPS) is a less-invasive alternative treatment option for patients with complications of portal hypertension. Successful outcomes in the management of recurrent variceal bleeding, refractory ascites, and hepatic hydrothorax have led to an increased use of TIPS over the past few years.[18-21] At the time of shunt placement, portosystemic pressure gradient (PSPG) can be measured, which provides an ideal method to quantify the impact of portal decompression on thrombocytopenia associated with liver cirrhosis.[22] To date, only a few studies on the effect of TIPS on platelet counts and the potential role of TIPS in the management of severe thrombocytopenia in the setting of cirrhosis have been published.[10,22-32] Most of these studies involved a relatively small number of patients, and the results are conflicting.

This article assesses the platelet response to TIPS and whether this response is related to other factors, such as the severity of pre-TIPS thrombocytopenia, pre- and post-TIPS PSPG, and the etiology of liver disease.

Materials and Methods

Ninety-two patients underwent a TIPS placement procedure at the Cleveland Clinic Foundation. Seventy-four of these patients were included in the study, and 18 were excluded. Exclusion criteria included: (1) death or orthotopic liver transplantation within 3 months of the TIPS placement procedure, (2) evidence of stenosis or occlusion of TIPS requiring revision or placement of a new shunt within 3 months of the procedure, (3) blood transfusion within 3 weeks of TIPS placement or within 3 months following the procedure, and (4) absence of necessary laboratory studies.

Platelet counts were measured on 3 different occasions over a 3-month period prior to the TIPS procedure as well as 3 times within 3 months following the procedure. Thrombocytopenia was defined as a platelet count of 150,000/mm^3 or less, moderate thrombocytopenia was defined as a platelet count of 100,000/mm^3 or less, and severe thrombocytopenia was defined as a platelet count of 50,000/mm^3 or less. A clinically significant platelet response to TIPS was defined as an increase in platelet count from pre-TIPS values of at least 20%.

The technical details of the TIPS procedure are described elsewhere.[23] The PSPG was measured prior to and immediately after placement of TIPS. The patency of the shunt was checked using Doppler ultrasound 24 hours and 3 months after the procedure. Doppler ultrasound was also performed whenever clinical symptoms, such as variceal bleeding or worsening of ascites, were suggestive of stent dysfunction.

Results are expressed as mean ± standard deviation (SD). Paired *t* test was used to compare platelet mean before and after the TIPS procedure. A *P* value of ≤.05 was considered statistically significant. Linear regression analysis was used to study the relationship between platelet count response (mean percentage increase after TIPS) and age, sex, etiology of liver disease, pre- and post-TIPS PSPG, post-TIPS decrease in PSPG, and pre-TIPS platelet count. All statistical analysis was performed using SAS statistical software (The SAS Institute).

Results

The demographics and clinical characteristics of the patients are shown in Table 1. Alcohol- and hepatitis C virus–induced cirrhosis were the 2 most common underlying etiologies for liver disease in this population (44/74; 60%), followed by cryptogenic cirrhosis (18/74; 24%). Patients with nonalcoholic steatohepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, congenital hepatic fibrosis, cardiac cirrhosis, and venoocclusive disease composed the remainder of the study population (10/74; 13.5%). The pre-TIPS mean PSPG ± SD was 23 ± 6 mm Hg, and the post-TIPS mean PSPG ± SD was 8 ± 3 mm Hg. The indications for TIPS were recurrent variceal bleeding in 45 of 74 patients (61%), refractory ascites and/or hepatic hydrothorax in 28 of 74 patients (38%), and thrombocytopenia in 1 of 74 patients (1%).

Table 1. Demographics and Clinical Characteristics of the Patients (N=74)

Age (yrs)	
Mean ± SD	59 ± 12
Range	24-87
Sex	
Male	34
Female	40
Etiology of Liver Disease[a]	
Alcohol-induced cirrhosis	23
Hepatitis C virus–induced cirrhosis	21
Cryptogenic cirrhosis	18
Nonalcoholic steatohepatitis	6
Primary biliary cirrhosis	4
Primary sclerosing cholangitis	3
Congenital hepatic fibrosis	1
Cardiac cirrhosis	1
Veno-occlusive disease	1
Portosystemic Pressure Gradient (mean ± SD)	
Pre-TIPS	23 ± 6 mm Hg
Post-TIPS	8 ± 3 mm Hg
TIPS Indications	
Recurrent variceal bleeding	45
Refractory ascites and/or hepatic hydrothorax	28
Thrombocytopenia	1

SD, standard deviation; TIPS, transjugular intrahepatic portosystemic shunt.

[a]Some patients have multiple diagnoses.

The mean ± SD platelet count for patients before and after TIPS placement was 100,000 ± 51,000/mm^3 and 114,000 ± 52,000/mm^3 (P<.0005), respectively, with a mean percentage increase in platelet count from pre- to post-TIPS of 22% for the entire group. Thirty-four of 74 patients (46%) had a clinically significant increase in their platelet count. When divided into subgroups based upon pre-TIPS platelet count, patients with moderate thrombocytopenia had a higher percentage of clinically significant response (25/40; 62%). The mean ± SD platelet count for patients in this subgroup before TIPS was 63,000 ± 19,000/mm^3, with a post-TIPS mean ± SD platelet count of 84,000 ± 30,000/mm^3 (P<.0005); the mean percentage increase in platelet count from pre- to post-TIPS was 36%. In patients with severe thrombocytopenia, 8 of 11 patients (73%) had a significant increase in platelet count. The mean ± SD platelet count for this subgroup before and after TIPS placement was 37,000 ± 7000/mm^3 and 57,000 ± 23,000/mm^3 (P<.0005), respectively, with a 55% increase in platelet count (Table 2 and Figure).

Linear regression analysis was used to examine the relationship between platelet count and TIPS. The pre-TIPS platelet count was found to be the best single predictor for the response to TIPS (r^2, 26.8; P<.001). Patients with lower pre-TIPS platelet count have the greatest platelet response to TIPS. Linear regression with stepwise selection was used to select additional variables for a multivariate model. No other variables were found to be a significant predictor for the platelet response to TIPS (Table 3).

Discussion

TIPS is a relatively new, minimally invasive treatment option for patients with variceal bleeding and refractory ascites. The effect of TIPS on thrombocytopenia associated with liver cirrhosis has not yet been adequately studied. There are few studies in the literature on the effects of TIPS on platelet counts, and the results are conflicting.

Since 1996, 8 studies have been published on the effect of TIPS on thrombocytopenia. Five of the studies reported significant change, and 3 reported no significant increase in platelet count after the procedure. In a retrospective study of 58 patients, Karasu and colleagues reported that TIPS had an unpredictable effect on platelet counts.[31] Of note, only a single platelet count reading was taken before the procedure, as well as 1 reading afterward. It is known that even among healthy individuals, platelet count shows a wide day-to-day variation (coefficient of variation, 6.1%).[23] Additionally, the pre-TIPS mean ± SD platelet count for patients in this study was higher than that in all other studies (120,000 ± 72,000/mm^3). In our study and studies by other groups, patients with a lower pre-TIPS platelet count were expected to have a higher increase in platelet count than patients with a higher pre-TIPS count. In a retrospective study by Jabbour and colleagues,[32] TIPS was reported to have no effect on thrombocytopenia, which was defined as a platelet count of less than 100,000/mm^3, with response to TIPS defined as a platelet count increase to more than 100,000/mm^3. Prior to TIPS placement, 50% of patients had thrombocytopenia; this percentage remained unchanged after the procedure. Thus, in that study, patients with a platelet count of 20,000/mm^3 or 30,000/mm^3 who had an increase in their platelet count to 80,000/mm^3 or 90,000/mm^3 (a significant increase) were considered nonresponders because their platelet count remained less than 100,000/mm^3. The third study that showed no significant increase in platelet count is a prospective study by Sanyal and colleagues.[26] It

Table 2. Effect of TIPS on Platelet Count

Patient Population	Number (%) of Patients Who Had Clinically Significant (≥20%) Increase in Platelet Count	Mean Platelet Count Before TIPS ± SD (in thousands/mm^3)	Mean Platelet Count After TIPS ± SD (in thousands/mm^3)	Mean % Increase	*P* Value
All patients, N=74	34 (46%)	100 ± 51	114 ± 52	22%	<.0005
Patients with moderate thrombocytopenia (platelet count ≤100,000/mm^3), n=40	25 (62%)	63 ± 19	84 ± 30	36%	<.0005
Patients with severe thrombocytopenia (platelet count ≤50,000/mm^3), n=11	8 (73%)	37 ± 7	57 ± 23	55%	<.0005

SD, standard deviation; TIPS, transjugular intrahepatic portosystemic shunt.

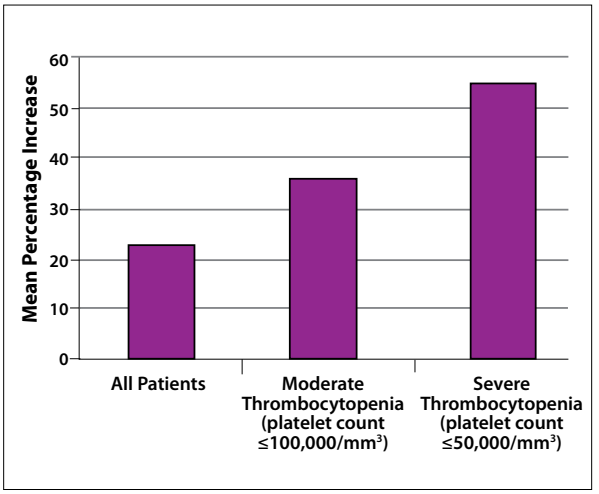

Figure. Percentage increase in platelet counts after TIPS.

TIPS, transjugular intrahepatic portosystemic shunt.

Table 3. Potential Predictors for Platelet Response to TIPS

Variable	*P* Value
Age	.1091
Sex	.8678
Pre-TIPS platelet count	<.001
Pre-TIPS PSPG	.8423
Post-TIPS PSPG	.8606
Decrease in PSPG	.8987
Percentage decrease of PSPG	.8494
Alcoholic liver disease	.9561
Hepatitis C virus	.7580
Nonalcoholic steatohepatitis	.9189

PSPG, portosystemic pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

is interesting that the mean ± SD pre-TIPS platelet count in that study was considerably low (58,000 ± 7,000/mm^3). With such a low platelet count, one might expect a significant increase in the post-TIPS count.

As mentioned above, 5 studies have shown a significant increase in post-TIPS platelet count. In a prospective, controlled study of 55 patients and 110 controls followed for 1 year, Gschwantler and colleagues reported an increase of 19.7% in post-TIPS platelet count.[22] In agreement with our study, a higher increase (25%) was noted in patients with low (≤100,000/mm^3) platelet count. The prospective study also reported that neither post-TIPS PSPG nor the degree of its reduction affects the post-TIPS platelet count. Pursnani and colleagues[24] reported an increase in post-TIPS platelet count in 34 of 45 patients (75%), with an increase in the mean ± SD platelet count from 83,000 ± 4000/mm^3 to 100,000 ± 5000/mm^3. Alvarez and colleagues reported a significant increase in the post-TIPS platelet count, which was persistent over 12 months of follow-up in a case series of 11 patients.[25] In a study by Lawrence and colleagues,[10] there was a significant increase in post-TIPS platelet count from 95,000 ± 44,000/mm^3 to 123,000 ± 91,000/mm^3. That study was the only one that showed a relationship between the post-TIPS PSPG and the post-TIPS platelet count, with a significant increase in the post-TIPS platelet count noted only when post-TIPS PSPG fell to less than 12 mm Hg. Jalan and colleagues[27] reported a platelet

increase following TIPS from a mean ± SD platelet count of 85,000 ± 8000/mm^3 to a mean ± SD platelet count of 135,000 ± 16,000/mm^3. This study was 1 of only 3 prospective studies. It included 23 patients with follow-up for a mean of 8 months. In concordance with our study, Jalan and colleagues[27] reported no relationship between the post-TIPS PSPG and the post-TIPS platelet count.

Our study confirmed the results of other studies that showed a significant increase in platelet count following TIPS.[10,22,24,25,27] Similar to results reported by Gschwantler and colleagues,[22] patients in our study with lower pre-TIPS platelet count had the greatest post-TIPS increase in platelet count. This finding conflicts with that of Lawrence and colleagues.[10] The explanation of this conflict is not clear; however, other studies have also failed to find such a connection.[22,27]

All of the studies on the effect of TIPS on platelet count showed that at least some patients would benefit from the procedure and have their platelet counts significantly increased. Who will benefit and whether any factors can predict patient response to TIPS are the main issues. In our study, a linear regression model was used to assess the effect of variables on the post-TIPS platelet response, including age, sex, indication of TIPS, underlying liver disease, pre-TIPS platelet count, and various combinations of PSPGs (before TIPS, after TIPS, change, and percentage change). We found only 1 predictor variable for the increase in platelet count (ie, the pre-TIPS platelet count), which was found to be inversely proportional to the percentage increase in post-TIPS platelet count, with the highest percentage increase occurring with the lowest platelet count.

Several studies have suggested that factors other than portal hypertension are involved in the pathogenesis of thrombocytopenia seen in cirrhosis. Thrombopoietin, a protein produced primarily in the liver, is thought to play an important role in the regulation of platelet production.[28] The production of thrombopoietin by the liver is decreased in cirrhosis; following liver transplantation, thrombopoietin levels increase.[30-32] Thrombopoietin levels are not expected to increase with TIPS. In fact, they may further decrease due to loss of hepatic parenchymal cell function induced by TIPS.[31] This may explain the decrease in platelet count noticed in some patients after the procedure. Other factors that may play a role in the pathogenesis of thrombocytopenia associated with liver cirrhosis include translocated toxin or other gut-derived substances,[32] antiplatelet antibodies,[7] and subclinical disseminated intravascular coagulopathy.[8,32]

The Model for End-Stage Liver Disease (MELD) score was originally introduced to predict mortality after the TIPS procedure.[33] The higher the MELD score, the higher the mortality after shunt placement. The effect of the MELD score on the platelet count change after TIPS is not known and was not investigated in this study, although it is an interesting issue that deserves further study.

Conclusion

Based on our study findings, TIPS may improve thrombocytopenia associated with liver cirrhosis. Patients with severe thrombocytopenia are more likely to benefit from this procedure. More studies are warranted to determine the potential role of TIPS in the management of thrombocytopenia associated with chronic liver disease.

The authors have no relevant conflicts of interest to disclose.

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