Gut and Gastroenterology

RESEARCH ARTICLE

Efficacy of Anticoagulation Therapy in Preventing Portal Vein Thrombosis Based on Blood Coagulation and Fibrinolysis Markers Following Partial Splenic Embolization

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Abstract

Background: This study investigated changes in blood coagulation and fibrinolysis markers and portal vein thrombosis rates in patients who underwent partial splenic embolization (PSE). After PSE, patients with portal hypertension were treated with gabexate mesilate (FOY) or recombinant thrombomodulin (rTM) with the aim of preventing portal vein thrombosis and localized disseminated intravascular coagulation (DIC).

Methods: PSE was performed for portal hypertension, and changes in coagulation markers including thrombin-antithrombin complex (TAT) and plasmin-α2-plasmin inhibitor complex (PIC) were analyzed in 36 patients. Twenty-one patients were treated with FOY, and 15 were treated with rTM. Clinical features, changes in post-PSE blood coagulation and fibrinolysis markers, presence or absence of portal vein thrombosis, and postoperative complications were compared between the groups.

Results: There were no significant differences between the FOY Group and the rTM Group in TAT, PIC, initial platelet count, age, underlying hepatic factors, spleen volume, or splenic infarction rate. In the rTM Group, no significant changes were seen in TAT or PIC before and after PSE, and there was no portal vein thrombosis. In the FOY Group, although there was no significant change in PIC after PSE, a significant elevation was seen in TAT, and portal vein thrombosis was seen in 3 (14.2%) of the 21 patients. Grade 2 vasculitis was seen in two patients in the FOY Group.

Conclusion: Administration of rTM may be a novel, safe, and effective to prevent portal vein thrombosis in PSE patients.

Keywords: Partial splenic artery embolization, Portal vein thrombosis, Thrombin-antithrombin complex, Pasmin-α2-plasmin inhibitor complex, Recombinant thrombomodulin, Gabexate mesilate

Introduction

Hypersplenism is a common manifestation of portal hypertension in liver cirrhosis [1]. The main treatments for hypersplenism with liver cirrhosis are splenectomy [2]. and partial splenic embolization (PSE) [3]. Portal vein thrombosis is a frequently seen complication with splenectomy, but it is rare with PSE rather than splenectomy [4].

However, once portal vein thrombosis occurs there is also a risk of liver failure, including impaired hepatic functional reserve [5, 6]. When performing PSE, consideration of preventive treatment for portal vein thrombosis is also an important issue. In splenectomy and PSE, various blood coagulation and fibrinolysis disorders, including localized disseminated intravascular coagulation (DIC), are potential causes of portal vein thrombosis.

Recently, thrombomodulin alfa (recombinant human soluble thrombomodulin: rTM; Asahi Kasei Phrama Corp., Tokyo, Japan) has been developed as a new drug for disseminated intravascular coagulation (DIC) [7, 8]. There have been many reports of the efficacy of rTM, but no studies have focused on the prevention of portal vein thrombosis in PSE.

In this study, the changes in blood coagulation and fibrinolysis markers and the portal vein thrombosis rates in groups administered gabexate mesilate (FOY) and rTM were investigated with the aim of preventing portal vein thrombosis and localized DIC in 36 patients who underwent PSE for portal hypertension.

Subjects and Methods

PSE was performed for portal hypertension, and changes in coagulation markers including thrombin-antithrombin

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complex (TAT) and plasmin-α2-plasmin inhibitor complex (PIC) were analyzed in 36 patients in our department from January 2013 to March 2019.

The subjects for this analysis were 21 patients in whom FOY (Ono Pharmaceutical, Osaka, Japan) was used and 15 in whom rTM (Asahi Kasei Pharmaceutical, Tokyo, Japan) was used after PSE. FOY (20-39 mg/kg) was administered by intravenous drip over 24 hours for 7 days, and rTM (380 U/kg) was administered by intravenous drip over 30 minutes for 7 days. Patients were divided into those who received FOY (Group A, N = 21) and those who received rTM (Group B, N = 15), and clinical features, changes in post-PSE blood coagulation and fibrinolysis markers, presence or absence of portal vein thrombosis, and postoperative complications were compared within and between the groups.

This study was approved by the Institutional Review Board of Saiseikai Niigata Hospital and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

Statistical Analysis

Prior to this study, all demographic and clinicopathological data had been prospectively collected in a computer database. Continuous variables were expressed as means ± standard deviation and compared by Student's t-test or the Mann Whitney U test. Variation in the descriptive variables was assessed using Wilcoxon rank-sum test. Values of $P < 0.05$ was considered statistically significant. Statistical analyses were performed using EZR ver. 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [9].

Results

Table 1 shows the patients' clinical features. There were no significant differences between the FOY Group and the rTM Group in TAT, PIC, initial platelet count, age, underlying hepatic factors, spleen volume, or splenic infarction rate (Table 2).

Platelet counts increased from 7.32 x10^4 /μL± 3.43x10^4 /μL to 16.06x10^4 /μL ± 5.21x10^4 /μL in rTM group as well as from 6.74x10^4 /μL± 2.92x10^4 /μL to 13.83x10^4 /μL±5.79x10^4 /μL in FOY group after PSE.

In the rTM Group, no significant changes were seen in TAT or PIC before and after PSE, and there was no portal vein thrombosis (Figure 1 and 2).

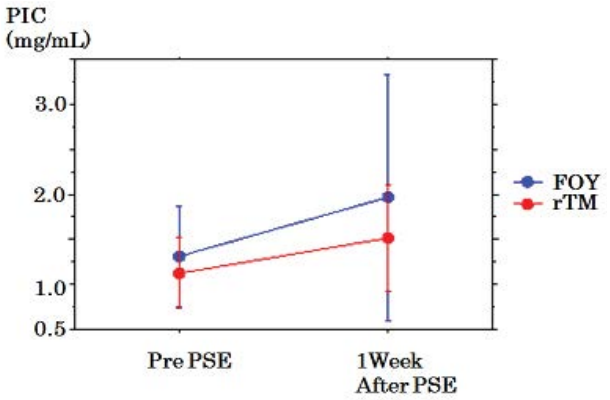

Figure 1: Comparison of PIC value between pre-PSE and post-PSE.

Table 1: Clinical features of partial splenic embolization

	mean±SD	Range
Age (years)	62.05 ±7.77	44-76
Gender (Male: Female)	22:14	
Etiology(B/C/Alc/NASH)	8/20/4/4	
Spleen Volume (ml)	438.75± 227.65	105- 1020.5
Infarction Volume(ml)	242.48± 139.63	21.15-626.63
Infarction Rate (%)	56.51±17.16	21.5-95.65
Platelet count (x10^4/μL)	7.42± 3.21	3.3-10.5
TAT (ng/mL)	3.13± 1.77	0.9-7.7
PIC (mg/mL)	1.23± 0.83	0.2-2.1

Table 2: Clinical features according to anti-coagulation therapy after partial splenic embolization

	FOY (n=21)	rTM (n=15)	P-value
Age (years)	60.28±8.34	64.53±6.37	p=0.107
Gender (Male: Female)	13:8	6:9	p=0.908
Etiology(B/C/Alc/NASH)	5/12/2/2	3/8/2/2	p=0.309
Spleen Volume (ml)	447.13±221.15	426.77±244.57	p=0.801
Infarction Volume(ml)	228.22±109.46	262.85±176.69	p=0.485
Infarction Rate (%)	53.51±14.53	60.79±20.14	p=0.228
Platelet count (x10^4/μL)	6.74± 2.93	8.33± 3.43	p=0.150
TAT (ng/mL)	3.41±1.81	2.75± 1.71	p=0.284
PIC (mg/mL)	1.31± 0.55	1.13± 0.38	p=0.294

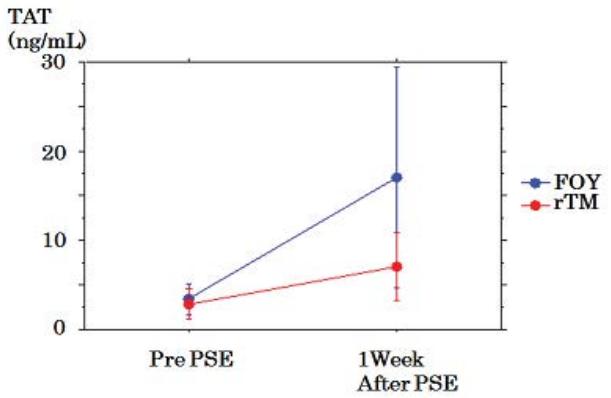

Figure 2: Comparison of TAT value between pre-PSE and post-PSE.

In the FOY Group, although there was no significant change in PIC after PSE, a significant elevation was seen in TAT (p=0.003), and portal vein thrombosis was seen in 3 (14.2%) of the 21 patients (Figure 1 and 2).

Grade 2 vasculitis was seen in two patients in the FOY Group, although no hemorrhagic symptoms were seen in either the FOY Group or the rTM Group.

Discussion

Hypersplenism is the condition in which splenomegaly develops with portal hypertension, resulting in pancytopenia [1]. Clinically, a tendency to bleed and various other symptoms appear, especially when platelets are decreased [10]. The spleen is understood to be an immune organ, but it also has blood filtration, storage, and hematopoietic functions. In treating hypersplenism, splenectomy has been done with the aims of improving hyperactivation of splenic function and lowering portal pressure. In recent years, interventional radiology has been developed as a less invasive treatment.

PSE has attracted attention as a method to preserve an important part of splenic function, improve hyperactivation of splenic function, and also lower portal pressure. This method was first performed by Maddison in 1973 as total splenic embolization in esophageal varix rupture patients in whom hemostasis was difficult with other conservative therapies [11]. There were several subsequent reports, but many patients experienced serious complications, including splenic rupture and splenic abscess. However, in 1979, Spigos reported that prophylactic administration of antibiotics and partial embolization were safe [12] after which serious complications decreased dramatically, and PSE has spread as a safe and reliable treatment. Regarding the usefulness of PSE, we previously reported that PSE can be expected to help maintain hepatic reserve [13].

Various blood coagulation and fibrinolysis disorders are thought to occur in relation to portal vein thrombosis following splenectomy and PSE in portal hypertension, including localized DIC with liver cirrhosis. Compared with splenectomy, there are thought to be fewer portal vein thrombosis complications with PSE, but they are not totally absent. The important thing is therefore to consider preventive treatment. Assuming that PSE itself induces localized DIC, performing treatment for DIC at an early stage is important in preventing portal vein thrombosis. Active administration of rTM or other anticoagulation therapies is useful against blood coagulation and fibrinolysis disorders, and it is thought to be desirable from the perspective of improving prognosis.

Thrombin-antithrombin complexes (TAT) were significantly higher in the thrombosis group after surgery [14]. Hence, PIC did not show significant changes in any chronic liver diseases [15].

In the present study, the changes in TAT and PIC indicate that PSE acts on hypercoagulation without causing increased activity of the fibrinolytic system, so that anticoagulation therapy is important.

Gabexate mesilate is a guanidino-fatty acid derivative in which the guanidino group binds noncovalently to the serine protease substrate binding site, reversibly inhibiting the interactions of enzyme and substrate. It was initially developed as a drug to treat acute pancreatitis due to its powerful anti-trypsin action, but it was also promising for an effect against DIC based on its anti-thrombin action [16].

On the other hand, rTM is an anticoagulant that has a novel action mechanism in which it binds specifically to thrombin, inhibiting its generation; it inhibits hypercoagulation and increased activity of the fibrinolytic system, and maintains the balance in the blood coagulation and fibrinolysis system after invasive treatments. In the present study, no significant changes were seen in blood coagulation and fibrinolysis system markers such as TAT and PIC after PSE in the rTM Group, and no cases of portal vein thrombosis were seen. This suggests that administration of rTM in PSE inhibits hypercoagulation, prevents fluctuation in TAT, and can prevent portal vein thrombosis. No adverse events associated with hemorrhage were seen before and after the administration of rTM, and there were not thought to be any major problems with safety.

From the present results it appears that administration of rTM may be a novel, safe, and effective way to prevent portal vein thrombosis in PSE patients who have a high risk of portal vein thrombosis. In the future, it will be necessary to investigate long-term outcomes in a large number of patients.

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Declaration of personal and funding interests

None.

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Abbreviations

PSE: partial splenic arterial embolization

References

1. Boyer TD, Habib S (2015) Big spleens and hypersplenism: fix it or forget it? *Liver Int* 35:1492-1498. [View Article]
2. Coon WW (1988) Splenectomy for thrombocytopenia due to secondary hypersplenism. *Arch Surg* 123:369-371. [View Article]
3. Sangro B, Bilbao I, Herrero I, Corella C, Longo J, et al. (1993) Partial splenic embolization for the treatment of hypersplenism in cirrhosis. *Hepatology* 18:309-14. [View Article]
4. Cai M, Zhu K, Huang W, Meng X, He K, et al. (2013) Portal vein thrombosis after partial splenic embolization in liver cirrhosis: efficacy of anticoagulation and long-term follow-up. *J Vasc Interv Radiol* 24:1808-1816. [View Article]
5. Intagliata NM, Caldwell SH, Tripodi A (2019) Diagnosis, Development, and Treatment of Portal Vein Thrombosis in Patients With and Without Cirrhosis. *Gastroenterology* 156:1582-1599. [View Article]
6. Mancuso A, Politi F, Maringhini A (2018) Portal Vein Thromboses in Cirrhosis: To Treat or Not to Treat? *Gastroenterology* 154:758. [View Article]
7. Mohri M, Sugimoto E, Sata M, Asano T (1999) Inhibitory effect of recombinant human soluble thrombomodulin on initiation and extension of coagulation. *Thromb Haemost* 82:1687-1693. [View Article]
8. Saito H, Maruyama I, Shimazaki S, Yamamoto Y, Aikawa N, et al. (2007) Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-bilind clinical trial. *J Thromb Haemost* 5:31-41 [View Article]
9. Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant.* 48 :452-458. [View Article]
10. Bashour FN, Teran JC, Mullen KD (2000) Prevalence of peripheral blood cytopenias (hypersplenism) in patients with nonalcoholic chronic liver disease. *Am J Gastroenterol* 95:2936-9. [View Article]
11. Maddison FE (1973) Embolic therapy of hypersplenism. *Invest Radiol* 8:280-281. [View Article]
12. Spigos DG, Jonasson O, Mozes M, Capek V (1979) Partial splenic embolization in the treatment of hypersplenism. *Am J Roentgenol* 132:777-82. [View Article]
13. Ishikawa T, Kubota T, Horigome R, Kimura N, Honda H, et al. (2014) Concurrent partial splenic embolization with transcatheter arterial chemoembolization for hepatocellular carcinoma can maintain hepatic functional reserve. *Hepatol Res* 44:1056-1061. [View Article]
14. Bezeaud, Denninger MH, Dondero F, Saada V, Venisse L, et al. (2007) Hypercoagulability after partial liver resection. *Thromb Haemost* 98:1252-1256. [View Article]
15. Ohmoto K, Yamamoto S, Ideguchi S, Yamamoto R, Takatori K, et al. (1990) Clinical significance of thrombin-antithrombin III complex and plasmin-alpha 2 plasmin inhibitor complex in chronic liver diseases. *Nihon Shokakibyo Gakkai Zasshi (in Japanese)* 87:1837-1845. [View Article]
16. Tamaki S, Wada H, Hiyoyama K, Shimura M, Minamikawa K, et al. (1993) Treatment of disseminated intravascular coagulation with gabexate mesilate. *Clin Ther* 15:1076-84. [View Article]

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