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EDITORIAL

Changing common sense: Anti-platelet/coagulation therapy against cirrhosis

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Abstract

Until recently, anti-platelet/coagulation therapy had not been recommended for patients with cirrhosis. Although venous thrombosis is one of the representative complications of cirrhosis and ischemic disorders associated with atherosclerosis are not infrequent in cirrhotic patients, many clinicians have tended to hesitate to introduce anti-platelet/coagulation therapy to their patients. Undoubtedly, this is due to the increased risk of hemorrhagic diathesis in cirrhotic patients. However, accumulating evidence has revealed the benefits of anti-platelet/coagulation therapy for cirrhotic patients. In addition to the safety of the therapy carried out against cardiovascular diseases in cirrhotic patients, some clinical data have indicated its preventive effect on venous thrombosis. Moreover, the efficacy of anti-platelet/coagulation therapy against cirrhosis itself has been demonstrated both clinically and experimentally. The conceptual basis for application of anti-platelet/coagulation therapy against cirrhosis was constructed through two pathologic studies on intrahepatic thrombosis in cirrhotic livers. It may be better to use thrombopoietin-receptor agonists, which have been tested as a treatment for cirrhosis-related thrombocytopenia, in combination with anti-platelet drugs to reduce the risk of venous thrombosis. During the last decade, the *World Journal of Gastroenterology*, a sister journal of *World Journal of Hepatology*, has been one of the main platforms of active discussion of this theme.

Key words: Anti-platelet/coagulation therapy; Cirrhosis; Hemorrhagic diathesis; Thrombosis; Thrombocytopenia

Core tip: Recognition concerning anti-platelet/coagulation therapy for cirrhotic patients has been changing from relative contraindication to recommendable. Administration of this type of drugs is expected to not only prevent cirrhosis-related thrombotic disorders but also slow down the progression of liver disease itself.

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PROLOGUE: CONTRAINDICATION?

Until recently, it was thought that a balance between the necessity and risks of anti-platelet/coagulation therapy for patients with cirrhosis had to be carefully considered. This therapy was believed to be rather a relative contraindication for cirrhotic patients. Even currently, no one can dispute that this therapy increases the risk of gastrointestinal bleeding in patients with advanced decompensated cirrhosis[1,2]. In contrast, venous thrombosis is one of important complications of cirrhosis[1-7]. In addition, cirrhotic patients who suffer from atherosclerotic cardiovascular and cerebrovascular diseases have been increasing in number with the prevalence of metabolic syndrome. As a result, a certain number of cirrhotic patients need anti-platelet/coagulation therapy. Many physicians seem to administer a minimum amount of anti-platelet/coagulation drugs to such cirrhotic patients very carefully but timidly.

The coagulation status of cirrhotic patients is certainly delicate and is placed on a very sensitive balance. Importantly, the balance easily leans towards coagulable as well as hemorrhagic[8-11].

DISCUSSIONS IN THE *WORLD JOURNAL OF GASTROENTEROLOGY* AND THE COAGULATION IN LIVER DISEASE STUDY GROUP

The accumulation of recent evidence through clinical observations and experimental investigations has been upsetting the hitherto common sense about anti-platelet/coagulation therapy for cirrhotic patients. Previous reports in this research field were mostly negative ones, which emphasized the risks and potential side effects of this therapy[12-14]. In 2003, however, a revolutionary research paper by Shi *et al*[15] published in the *World Journal of Gastroenterology* (*WJG*), a sister journal of the *World Journal of Hepatology* (*WJH*), reported the efficacy of heparin administration to cirrhotic patients. Thereafter, papers suggesting the safety and benefits of anti-platelet/coagulation therapy for cirrhotic patients have been published[6-8,16-30].

An international workshop of the Coagulation in Liver Disease Study Group (CLDSG) established by Professor Caldwell at the University of Virginia, has been promoting this movement. Since 2005, every other year this group has held a symposium with heated discussions to form a consensus for the best management of liver-related coagulation disorders[9,20,21]. Their latest conclusion states that anti-platelet/coagulation therapy is applicable as a treatment and preventive tool for cirrhotic patients although sufficient prophylactic means against gastrointestinal bleeding are required.

After the article of Shi *et al*[15], *WJG* has steadily published further articles suggesting the benefits of this therapy[2,5-8,16,17,22,31,32]. Some papers in *WJG* have discussed the efficacy of this therapy not only for thrombotic complications but also for the diseased liver itself[3,6,17]. The journal and its contributors possessed amazing prospective insight; they were approximately 4 years ahead of analogous publications in other journals[18-20].

THE SOURCE OF THE IDEA

Undoubtedly, two papers written by Wanless *et al*[33,34] and published in 1995 are the source of the present idea that anti-platelet/coagulation therapy may be beneficial for cirrhotic patients. They demonstrated both macroscopically and histologically the presence of intrahepatic thrombi in cirrhotic livers, and suggested that the thrombi potentially contribute to further liver damage (*i.e.*, parenchymal extinction) and to the development and progression of portal hypertension. Subsequently, relevant data indicating abnormal intrahepatic platelet aggregation in cirrhotic patients have been published[20,35,36]. These papers disclose a part of the mechanisms of cirrhosis-related thrombocytopenia, and prove the usefulness of anti-platelet/coagulation therapy for cirrhotic patients.

THROMBOPOIETIN RECEPTOR AGONISTS

As the latest subject in this research field, we refer to clinical trials of administration of thrombopoietin receptor agonists (eltrombopag and avatrombopag) to cirrhotic patients with thrombocytopenia[37-40]. The aim of the interventional trials is to expand the indication of antiviral therapies and invasive procedures for cirrhotic patients[39,40]. These agents obviously increase the circulating platelet count through direct stimulation of thrombopoiesis. Similar to splenectomy for cirrhotic patients, the theoretical background seems to be simple and to make sense. However, since the projects lacked enough insight into coagulation abnormalities of cirrhotic patients, many patients developed portal vein thrombosis[40]. A member of the CLDSG immediately pointed out the significant risk of hypercoagulable complications introduced by non-selective administration of thrombopoietin receptor agonists[41]. A similar discussion was presented in the recent issue of *WJG*[42].

Because the etiology of cirrhosis-related thrombocytopenia is quite diverse[32,36,43,44], forcible normalization of the platelet count targeting only one factor may be either ineffective or even risky. Our recent data[44] suggest that at least three major factors, including decreased thrombopoiesis, hypersplenism and excessive platelet aggregation, contribute to the development of

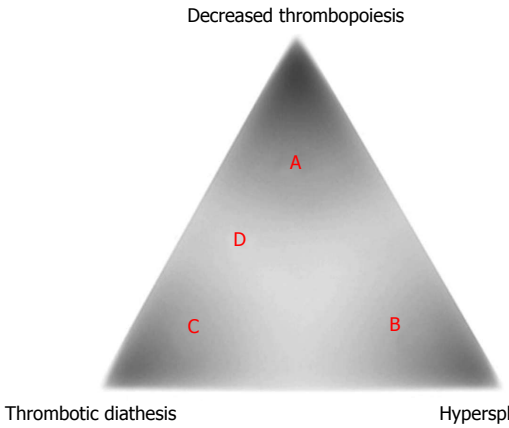

Figure 1 Theoretically ideal therapies against cirrhosis-related thrombocytopenia depending on the etiology. The platelet count in cirrhotics is determined mainly by three major factors, including (A) a rate of thrombopoiesis, (B) the presence/abscence of hypersplenism, and (C) the presence/abscence of thrombotic diathesis, which differently affect each case. Patients with thrombocytopenic conditions A, B, or C are considered to respond well to thrombopoietin receptor agonists, splenectomy, and anti-platelet/coagulation drugs, respectively. In patients with condition D, a combination of thrombopoietin receptor agonists and anti-platelet/coagulation drugs is thought to be necessary.

cirrhosis-related thrombocytopenia (Figure 1). Hence, normalization of the platelet count is thought to require a correct diagnosis of each patient's background conditions leading to thrombocytopenia and strict selection of the appropriate method for each case. In some cases, a combination of multiple methods may lead to a favorable outcome (Figure 1). To construct such a combination therapy, anti-platelet/coagulation therapy is a key element, and needs an approval to the extended application against cirrhosis.

EPILOGUE: TO BE APPROVED AS AN ALTERNATIVE THERAPY

Because platelets are very small blood cells without nuclei and are hardly detected by an ordinary histological examination (Figure 2), their pathological significance in diseases other than vascular disorders has seldom been considered. They play an important role in many inflammatory disorders as a mediator of both inflammatory reactions and fibroproliferative reactions. If hepatologists can correctly understand the robust pathobiological faculties of platelets, a dramatic paradigm shift will be approaching. Anti-platelet/coagulation therapy is not a novel medical tool, and past clinical research suggested the ineffectiveness of this therapy for cirrhosis[45]. However, it should be considered as one of the treatment options for cirrhosis again in this era in which antiviral therapies have sufficiently been developed.

We strongly hope and expect that *WJH* and its sister journal *WJG* will continue to be a discussion platform for and a witness of this changing common sense concerning anti-platelet/coagulation therapy against cirrhosis.

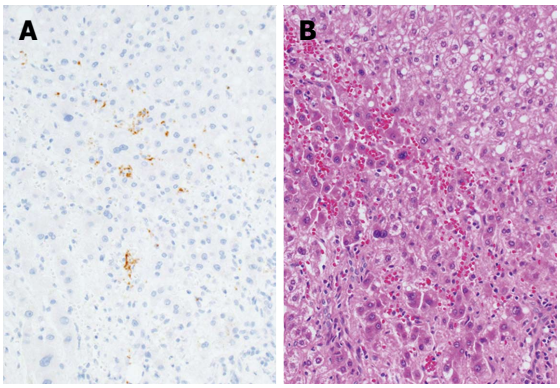

Figure 2 Platelet aggregation in a cirrhotic liver. A: Immunohistochemical findings. Platelets are stained in brown. (Immunoperoxidase for CD41; original magnification, × 400); B: The corresponding histological findings. Platelets cannot be identified in this photomicrograph. (Hematoxylin-eosin; original magnification, × 400).

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