



Effects of anticoagulants in patients with cirrhosis-related portal vein thrombosis

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Anticoagulation has been recommended for the primary management of portal vein thrombosis (PVT), and the purpose of anticoagulation therapy is to prevent the extension of thrombosis and to improve recanalization (40–80%) (1). Low molecular weight heparin (LMWH) is widely used as a front-line therapy to induce rapid anticoagulation. Different from non-cirrhotic patients, PVT is common in cirrhotic patients despite the clinical manifestation of hypocoagulable state and thrombocytosis (2).

In the *Gastroenterology* (3), Loffredo *et al.* published their meta-analysis results of 353 patients across eight recent studies (four from Western countries and four from Asian countries) to investigate the role of anticoagulation therapy in cirrhosis-related PVT. In their results, anticoagulation therapy increases recanalization (71% *vs.* 42%, $P < 0.001$) and reduces progression (9% *vs.* 33%, $P < 0.001$) of thrombosis comparing to the untreated groups. Loffredo's results also conclude that there is no difference in major and minor bleedings (11% *vs.* 11%) and lower incidence of variceal bleeding (2% *vs.* 12%, $P = 0.04$) among the treated and untreated groups.

Heparin is widely used as an anticoagulant agent for PVT, deep vein thrombosis, pulmonary embolism and thrombophlebitis. Heparin binds and activates anti-thrombin III to inactivate thrombin, factor Xa and other proteases and prevents clot formation (4). In addition to its anticoagulation effect, heparin mediates cellular cross-talk and signaling to modulate biological activities including angiogenesis, cell proliferation and inflammation (5). Heparin binds to many extracellular proteins and growth

factors including heparin-binding EGF-like growth factors; and the heparin-binding EGF-like growth factors are potent inducers of neovascularization and wound healing (6). In addition, the angiogenic role of heparin may improve the recanalization of PVT. It is further shown by Loffredo's results that LMWH, but not warfarin, is associated with a complete PVT resolution.

The incidence of PVT among Western cirrhotic patients is as high as 10–25%; and 22–28% of PTV patients have underlying cirrhosis. (7) Different from the Western patients, the Asian cirrhotic patients have relatively lower incidence of PVT. In an angiographic study (8), only 0.573% of the 708 Japanese cirrhotic patients developed PVT; and most of the PVT cases were associated with past splenectomy. These findings are consistent with a lower incidence of deep vein thrombosis and pulmonary embolism after knee arthroplasty in Asians (9).

In Europe, PVT is often caused by thrombotic tendency such as polycythemia vera, thrombocytosis, and G20210A polymorphisms of the prothrombin gene and T677T of the methylenetetrahydrofolate reductase gene (MTHFR) (10). However, the G20210A prothrombin variant is not detected in the Asian-Pacific Region; the T677T and C677T genotypes of the *MTHFR* gene in the Asian-Pacific region are not associated with deep vein thrombosis (11). Therefore, most Asian PVT cases are related to other factors such as malignancy, abdominal surgical interventions (e.g., splenectomy, sclerotherapy), pancreatitis, and drugs (e.g., oral contraceptives, overt diuresis). It is interesting that the thrombotic changes in

response to LMWH therapy are not different between the Western and Asian studies despite different pathogenesis.

Asian-Pacific region has a very high prevalence of viral hepatitis, cirrhosis and hepatocellular carcinoma (HCC). Patients with post-necrotic cirrhosis often progress to HCC, and patients with invasive HCC may develop tumorous thrombi within the portal vein (12). It is thus important to screen for HCC and to differentiate the cause of portal vein thrombi before LMWH therapy. Image-guided percutaneous fine needle aspiration or biopsy as well as contrast-enhanced ultrasonography (sensitivities of 82.5–98%), computed tomography (68–86%) or magnetic resonance (92–95%) may help with the differential diagnosis of tumorous thrombi and the extent of thrombosis (13).

In conclusion, LMWH therapy is safe and effective for increasing recanalization and preventing progression of PVT. LMWH therapy, but not warfarin, is associated with a complete PVT resolution. The thrombotic changes in response to LMWH therapy are similar among Western and Asian studies despite different pathogenesis. Asian patients having PVT are recommended to exclude tumorous thrombi before administering LMWH therapy.

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