Title :Efficacy and Safety of Nadroparin Calcium-Warfarin Sequential Anticoagulation in Portal Vein Thrombosis in Cirrhotic Patients：A Randomized Controlled Trial

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Study Protocol

All patients admitted at the Gastroenterology Department of the Qilu Hospital of Shandong University in China, who were diagnosed with PVT, were prospectively and consecutively evaluated in this study. The inclusion criteria were the following: age between 18 and 75 years, liver cirrhosis diagnosis based on clinical, laboratory and imaging studies, PVT diagnosed by abdominal contrast-enhanced computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI) or portal angiography. The exclusion criteria were the following: cavernous transformation of the portal vein, uncontrolled active bleeding, platelet count lower than 10∗10^9/L, creatinine more than 170 μmol/L, ongoing or received antithrombotic/thrombolytic treatment, primary thrombophilia, Budd-Chiari syndrome, pregnancy or breast-feeding period, severe cardiopulmonary diseases, severe systemic infection or sepsis, and inability to sign the informed consent.

Eligible patients were randomly divided into two equal groups: NWS therapy group and control group. Randomization was performed using a computer-based random number table procedure. Randomly generated serial numbers were placed in opaque envelopes. Patients and clinicians carrying out the interventions were not blinded, while clinicians performing the imaging assessments and data analysis were blinded to the group allocation and patients' coded data.

Procedure

The NWS therapy group received a subcutaneous injection of nadroparin calcium every 12 h for 1 month followed by an oral administration of warfarin for 5 months.

Warfarin was started at least 5 days before nadroparin calcium was stopped. International normalized ratio (INR) was monitored every 3-4 days and the daily dose of warfarin was carefully adjusted by the increase or decrease of 0.75 mg until the INR target level of 2-3 was achieved. Patients in the control group did not receive any anticoagulation treatment.

All patients underwent gastroscope to evaluate the degree of varices and received endoscopic ligation or sclerotherapy if necessary. Patients in the NWS therapy group initiated the anticoagulation therapy after endoscopic therapy.

Imaging studies

PVT assessed by imaging examination appears as the absence of flow in part or all the lumen of the splenoportomesenteric axis, including portal vein trunk and branches, SV or SMV, with the presence of solid material in the vein. The degree (partial occlusion or complete occlusion) and extension (portal vein only or extension into the SV and/or SMV) of PVT were also evaluated in all the enrolled patients at admission by upper abdominal contrast-enhanced CT or MRI or portal angiography. The assessments of thrombosis were based on a published study(22). For each venous segment, the vein and residual patent lumen were outlined at the level of the maximum thrombosis. Total lumen area and patent lumen area were calculated with commercially available software. The degree of thrombus occlusion was estimated as a percentage by thrombosis area/total lumen area×100%(22). The extension of thrombosis was referred to the involved segments of the portal vein system, regardless of whether thrombosis was formed in the portal vein only or extended into the SMV and/or SV(23, 24).

Complete and partial thrombosis were defined as equal or greater than 90% and less than 90% thrombotic material presence within vessels, respectively. Although the imaging assessments were performed by a single reader, the bias is minimized as the calculated assessments are objective.

Follow-up

Follow-up visits were scheduled at the 0^{th} and 6^{th} month, and included clinical, laboratory and imaging evaluation. The follow-up started at the diagnosis of PVT, defined as starting on the date of the first radiological imaging documenting PVT, and stopped in January 2020 or the day of death or the date of the last visit at 6^{th} month. Liver function and cirrhosis severity were assessed by Child-Pugh score and the Model for end-stage liver disease (MELD) score respectively at the 0^{th} and 6^{th} month.

Bleeding episodes were assessed every month by phone call. Once a severe bleeding episode occurred, the anticoagulation treatment was stopped immediately and endoscopic therapy was performed if necessary.

Outcomes and definitions

The primary outcome was the overall recanalization rate, both complete and partial. The secondary outcomes were bleeding rates, consisting of rates of hematemesis, melena, epistaxis, injection-site hemorrhage and other bleeding events.

Portal vein recanalization was evaluated on the basis of imaging examination. Complete recanalization was referred to the complete disappearance of the thrombus in the portal vein trunk, at least one of the two intrahepatic portal vein branches, SMV and SV. Partial recanalization was defined as a more than 50% reduction of the thrombus,

with the thrombus not extending to other veins. No response or stable thrombosis was defined when the thrombus maintained the same dimension, or achieved a less than 50% decrease or less than 30% increase on cross section. Progression was defined as more than 30% increase of the thrombus than before or thrombus extended to unaffected segments of the splenoportomesenteric axis (Fig. 1).

Group size calculation

The overall recanalization rate of the PVT at the 6^{th} month was chosen as the primary outcome to calculate the size of the groups. Based on previous studies (25), assuming a 30% difference in the overall recanalization of PVT at 6^{th} month between the anticoagulation (70%) and control group (40%), 5% α and 20% β error, 27 patients were needed in each group. Considering a 10% dropout rate, 30 patients should be included in each group.