Safety and Efficacy of Anticoagulation Therapy With Low Molecular Weight Heparin for Portal Vein Thrombosis in Patients With Liver Cirrhosis

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Background: Treatment of portal vein thrombosis (PVT) in patients with liver cirrhosis is not well established.

Aim: We intended to assess the safety and efficacy of low molecular weight heparin (LMWH) to treat PVT in cirrhotic patients.

Study: All 39 patients diagnosed with non-neoplastic PVT and cirrhosis from June 2005 to December 2006 were evaluated for anticoagulation therapy (AT). PVT was occludent in 15.4%, partial in 64.1%, and portal cavernoma presented in 20.5%. Twenty-eight patients received 200 U/kg/d of enoxaparin for at least 6 months. In 39.3% of patients PVT was an occasional finding, in 10.7% presented with acute abdominal pain, in 50% with bleeding from gastroesophageal varices. In this last group LMWH was started after endoscopic eradication of varices by band ligation.

Results: Complete recanalization of portal vein occurred in 33.3%, partial recanalization in 50% and no response in 16.7% of patients. Further 12 patients who continued AT obtained complete recanalization at a median time of 11 months (range 7 to 17 mo). Overall, a complete response was obtained in 75% of patients. No significant side effects, particularly bleeding complications, were observed during the treatment.

Conclusions: LMWH demonstrated safe and effective in the treatment of PVT in patients with liver cirrhosis.

Key Words: portal vein thrombosis, cirrhosis, anticoagulation, heparin

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Portal vein thrombosis (PVT) can be considered a complication of liver cirrhosis, frequently associated with hepatocellular carcinoma (HCC). The prevalence of non-neoplastic PVT in patients with liver cirrhosis ranges from 8.4% to 15%.1,2

The decreased velocity of portal flow is the main pathogenetic factor even if other thrombophilic causes, congenital or acquired, can concur. The occurrence of PVT leads to a deterioration of liver disease through a further increase of portal hypertension and impairment of liver perfusion with a decrease in liver functional reserve.3

The extension of thrombosis to splenic or mesenteric veins can determine, even if rarely, fatal complications as splenic or intestinal infarction.4 Moreover, complete occlusion of the portal, splenic, or mesenteric axis represents a challenge for the transplant surgeon, and is associated with an increased posttransplantation morbidity and mortality.1,5

Anticoagulation is considered, to date, the therapy of choice in patients with noncirrhotic portal vein occlusion.6 It is able to obtain partial or complete venous recanalization in 45% to 92% of cases of recent thrombosis.7,9 Moreover, the therapy results are safe as it does not increase the number and severity of hemorrhagic complications of portal hypertension.6

Concerns of anticoagulation therapy (AT) of PVT in patients with liver cirrhosis are founded on the high risk of bleeding related to clotting impairment and portal hypertension.

Recent studies show that the alterations of classical coagulation tests do not reflect the bleeding risk in cirrhosis and a balance between pro and anticoagulant factors, even if underscored, is present till advanced stages of liver disease.10

From a clinical standpoint, the risk of venous thromboembolism in patients with liver cirrhosis is showed to be the same as the general population.11

Only one study on AT in cirrhotic patients with PVT has been published so far,1 and the recent guidelines of AASLD on vascular liver disorders do not provide recommendations for this specific group of patients.12

The aim of our pilot study was to explore the safety and efficacy of AT with low molecular weight heparin (LMWH) of PVT in patients with liver cirrhosis.

PATIENTS AND METHODS

From June 2005 to December 2006, all patients with liver cirrhosis admitted to the Unit of Gastroenterology of A. Cardarelli Hospital in Naples received Doppler ultrasound examination as a part of routine work up. In the presence of PVT spiral CT or magnetic resonance was performed to exclude concomitant HCC and to evaluate the extension of thrombosis to portal-splenic-mesenteric axis. Thrombosis was considered occludent when thrombus involved more than 75% of the vessel and blood flow was absent or minimal.

All patients with diagnosis of PVT were included in the study and were evaluated for AT. The study protocol was approved by local ethics committee. HCC, cavernomatous transformation of portal vein, advanced liver
disease (Child-Pugh C) not suitable for liver transplanta-
tion were considered exclusion criteria. After written
informed consent was obtained from each patient, LMWH
(enoxaparin, 200 U/kg/d) was administered subcutaneously
for at least 6 months.

Patients who were admitted because of variceal
bleeding started AT after endoscopic eradication of varices
by ligation and β-blocker prophylaxis of rebleeding.

In other patients with medium-large varices β-blockers
were given if not contraindicated.

Patients were seen every month and submitted to
biochemical evaluation and Doppler ultrasound examina-
tion; spiral CT was performed at sixth month.

We considered complete “response” when complete
recanalization of the vessel was obtained, partial response
when a reduction of more than 50% of the thrombus was
observed, and “no response” in the other cases was
observed.

In the case of complete recanalization of the portal
vein or no response anticoagulant therapy was stopped at
the sixth month. Patients with partial response on waiting
list for liver transplantation or with intestinal ischemia
were continued on AT.

RESULTS

Among 373 patients with liver cirrhosis admitted
during the study period, 78 (21%) had HCC. Of the
remaining 239 patients, 39 (13.2%) had PVT, of these 8
(20.5%) were with portal cavernoma. Three patients with
PVT had advanced liver disease but were excluded from
liver transplantation (2 because they were older than 65
years, 1 had extrahepatic cancer).

Twenty-eight patients received AT. Their median age
was 55.5 years, 46.4% of the patients were in Child-Pugh
class B/C, 14 (50%) patients had ascites, 2 (7.1%) had
hepatic encephalopathy. Nine patients had earlier bleeding
from portal hypertension and 7 had received endoscopic
treatment.

Portal thrombosis was occludent in 5 of 28 patients
(16.7%) and was partial in 23 patients (83.3%). Concomi-
tant mesenteric involvement was present in 15 patients
(55.5%) and was occludent in 6 patients. Splenic thrombo-
sis was found in further 5 cases (16.7%).

Fourteen patients (50%) were admitted because of
acute bleeding from esophageal or gastric varices, 3 patients
(10.7%) for acute abdominal pain whereas PVT was an
occasional finding in the remaining 11 patients (39.3%).

AT was started at clinical presentation in patients who
were asymptomatic and with acute abdominal pain whereas
in patients with bleeding, AT was delayed till eradication
of varices was obtained. It occurred at a median time of
4 months from PVT diagnosis.

After 6 months of AT, 9 (33.3%) patients obtained
complete recanalization of PVT whereas no response was
observed in 5 patients (16.7%); in both cases AT was
stopped.

In the remaining 14 patients with a partial response
AT was continued: in 2 patients because of intestinal
ischemia at presentation and in 12 waiting for liver
transplantation. In this group, 12 (85.7%) patients achieved
complete recanalization in a median time of 11 months
(range 7 to 17 mo).

Overall, 21 of 28 patients (75%) obtained complete
recanalization in a median time of 6.5 months (range 1 to
17 mo). Figure 1 shows the cases of a complete and a partial
response to AT. No differences in clinical features and
extension of portal thrombosis were seen in patients who
were early or late responders and those that were non-
responders to AT.

No patients presented severe side effects of AT,
which required interruption of therapy; two patients pre-
sented mild anemia due to severe hypertensive gastropathy.
requiring iron supplements. The drop of hemoglobin levels was 1.5 and 2 g/dL, respectively. In the remaining patients hematocrit levels did not modify during the treatment: the basal and end-treatment levels were 31 (25-45) and 32.3 (25-40), respectively. One patient complained of transient diarrhea and 1 of pruritus. The median value of platelets was 59,000/mmc (range 23,000 to 138,000) and 58,000/mmc (range 24,000 to 131,000) respectively, before and at the end of AT. Despite being low, the number of platelets did not change significantly in each patient during AT treatment.

During the follow-up PVT progressed in 2 of the 5 patients who were nonresponders to AT, 1 had involvement of the mesenteric vein, and the other 1 developed portal cavernoma. Of the 21 patients who achieved a complete recanalization 2 died of liver-unrelated causes (lymphoma 1, cardiac infarction 1) and 2 because of liver decompensation, 2 patients were transplanted. Four are still on AT, 2 for previous mesentric ischemia and 2 awaiting liver transplant.

Three of the 11 remaining patients who stopped AT showed rethrombosis in the portal vein at 1, 4, and 24 months. These events were diagnosed while the patients were asymptomatic during the follow-up.

DISCUSSION

The treatment of deep vein thrombosis and pulmonary embolism is well established and evidence-based guidelines are regularly updated whereas the management of splanchnic vein thrombosis is not validated, given the rarity of the disease, and also the recent published guidelines are based on a low grade of evidence.

Even fewer data are available on the treatment of non-neoplastic PVT in patients with liver cirrhosis and currently the management of this disease is based on individual experience. Concerns exist for treating patients at risk of bleeding as cirrhotics because of coagulopathy and portal hypertension. Indications for treatment are not yet well defined because the impact of portal thrombosis on the natural history of liver disease is largely unknown. Systemic or local thrombolysis, AT, and transjugular intrahepatic portosystemic shunt have been reported in a few series.

In the setting of liver disease it is necessary to show convincing and definitive safety of any treatment before discussing indications for therapy of PVT. The next step should be to study the long-term effect of treatment of PVT on the prognosis of liver disease.

We chose LMWH to treat PVT in a group of patients with liver cirrhosis for a number of reasons: first, the drug was shown to be effective and safe in the treatment of other vein thromboses, second, the anticoagulant effect is rapidly reverted in case of hemorrhagic complications, mainly bleeding from gastroesophageal varices; third, the therapeutic range of oral anticoagulation is not validated in cirrhotic patients; and fourth, patients may present spontaneously high levels of PT-INR, already >2.

Our hospital is a regional referral center for liver transplantation, bleeding in cirrhotic patients, and splanchnic thrombosis and this may explain the high number of bleeding patients (50%) in our group. AT was offered to patients who wee candidate to OLT and in patients who presented with acute PVT or symptomatic mesenteric involvement. Moreover, we included a group of young patients with compensated liver cirrhosis but presenting with a complication of portal hypertension as bleeding from gastroesophageal varices. In this last group AT was performed to prevent progression of PVT precluding future options of OLT as well.

After 6 months of AT we obtained a complete recanalization in 33.3%, partial recanalization in 50%, and no recanalization in 16.7% of patients. Overall the response to AT was 73.3%, a rate similarly reported by Condat et al who obtained partial or complete recanalization in 92.5% of 27 patients with recent noncirrhotic PVT.

Twelve patients with a partial response continued AT and further 10 patients obtained a complete venous recanalization in a median time of 11 months; therefore 75% of 28 patients obtained a complete response to AT.

This rate of response is higher than that reported in patients with noncirrhotic PVT in which complete recanalization is reported in 37% to 45.4% and it could be explained by earlier diagnosis of PVT in cirrhosis, frequent association with multiple thrombophilic factors in non-cirrhotic patients, and finally the prolonged time of AT in our patients.

The only study dealing with AT in cirrhotic PVT reported a complete response in 42.1% of patients awaiting liver transplantation and treated with oral anticoagulants for a median of 4.7 months. We can argue the shorter duration of anticoagulation in the study of Francoz et al. might explain the difference in the complete recanalization rate.

Our data suggest that AT is effective in cirrhotic PVT but has to be administered for a period longer than 6 months to obtain complete recanalization. In our group of patients with PVT portal cavernoma was present in 20.5% whereas it is present in about 50% of patients with noncirrhotic PVT. This difference could be explained by the fact that PVT is diagnosed earlier in cirrhotic patients who are frequently submitted to medical and imaging evaluation.

In patients with liver cirrhosis portal cavernoma is to be considered the only sign of old thrombosis as hypersplenism and collateral vessels are already part of portal hypertension features.

Despite acute clinical onset we could not establish the date of occurrence of PVT in our patients, and in more than 50% the start of AT was delayed by a median of 4 months till the eradication of esophageal varices. This delay did not influence the efficacy of AT.

LMWH was shown to be safe and well tolerated in our patients and only minor and transient side effects were observed in 2 patients who did not require interruption of therapy. As no new bleeding or rebleeding episodes occurred in patients with esophageal varices at risk or bleeding from varices at admission observed for a mean period of 24 months, a favorable effect of AT can also be hypothesized.

This study would like to assess the safety and efficacy of the treatment of PVT in cirrhotic patients. We showed that LMWH is safe and effective in obtaining recanalization of the portal vein in patients with cirrhosis.

The benefits of recanalization of an occluded vein are shown thus far only in patients waiting for liver transplantation as a patent vessel makes simpler the operative procedure and consequently reduces the morbidity and mortality post-OLT. It is an obvious indication of treating
acute symptomatic PVT with mesenteric involvement because of the risk of intestinal infarction.  

In the other cases the beneficial effects of PVT recanalization are not shown even if the resolution of a portal thrombosis could prevent further deterioration of liver function or the increase in portal hypertension.  

Our preliminary study has the limitations of a noncontrolled study. Nevertheless, it shows the safety of anticoagulant treatment and allows planning of controlled studies that could identify which patients with cirrhotic PVT can benefit from AT.

REFERENCES