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BRIEF ARTICLE

Prophylaxis for venous thromboembolism after resection of hepatocellular carcinoma on cirrhosis: Is it necessary?

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Abstract

AIM: To assess the safety and effectiveness of prophylaxis for venous thromboembolism (VTE) in a large population of patients with hepatocellular carcinoma (HCC) on cirrhosis.

METHODS: Two hundred and twenty nine consecutive cirrhotic patients with HCC who underwent hepatic resection were retrospectively evaluated to assess whether there was any difference in the incidence of thrombotic or hemorrhagic complications between those who received and those who did not receive prophylaxis with low-molecular weight heparin. Differences and possible effects of the following parameters were investigated: age, sex, Child-Pugh and model for end-stage liver disease (MELD) score, platelet count, presence of esophageal varices, type of hepatic resection, duration of surgery, intraoperative transfusion of blood and fresh frozen plasma (FFP), body mass index, diabetes and previous cardiovascular disease.

RESULTS: One hundred and fifty seven of 229 (68.5%) patients received antithromboembolic prophylaxis (group A) while the remaining 72 (31.5%) patients did not (group B). Patients in group B had higher Child-Pugh and MELD scores, lower platelet counts, a higher prevalence of esophageal varices and higher requirements for intraoperative transfusion of FFP. The incidence of VTE and postoperative hemorrhage was 0.63% and 3.18% in group A and 1.38% and 1.38% in group B, respectively; these differences were not significant. None of the variables analyzed including prophylaxis proved to be risk factors for VTE, and only the presence of esophageal varices was associated with an increased risk of bleeding.

CONCLUSION: Prophylaxis is safe in cirrhotic patients without esophageal varices; the real need for prophylaxis should be better assessed.

Key words: Hepatic surgery; Hepatocellular carcinoma; Liver cirrhosis; Postoperative bleeding; Postoperative thromboembolism; Venous thromboembolism prophylaxis

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INTRODUCTION

Venous thromboembolism (VTE) is a significant cause of morbidity and mortality in patients who have undergone open gastrointestinal surgery, particularly if they were operated on due to malignancy[1,2].

Hepatocellular carcinoma (HCC) is the most frequent primary neoplasm of the liver and often develops as a consequence of chronic liver disease[3]. It is well known that several hemostatic alterations are present in patients with liver disease: primary hemostasis is often impaired due to piastrinopenia and secondary hemostasis can be hampered by the reduced synthesis of coagulation factors that normally takes place in the liver[4]. These alterations can be worsened by the decrease in hepatic volume caused by hepatic resection. A historical series of cirrhotic patients undergoing liver resection reported an 8.4% incidence of hemorrhagic complications following surgery[5].

While there is currently agreement on the need for pharmacological prophylaxis of VTE in surgical patients in general, little is know about the effect of this prophylaxis in patients with chronic liver disease who undergo hepatic resection due to the presence of HCC.

Studies on the coagulative pattern have shown that in patients with chronic liver disease there is decreased production of natural anticoagulant proteins that could result in an increase in the risk of thrombotic events; however, in clinical studies the incidence of VTE in cirrhotic patients seems to be lower than in the general medicine population[6].

Although great advances have taken place in the field of hepatobiliary surgery, resection of a cirrhotic liver remains a challenging procedure and hepatic surgeons may not feel confident in administering antithromboembolic prophylaxis to patients who have an increased risk of bleeding.

In our centre, where a large number of hepatic resections are performed, we have more and more frequently adopted a scheme of prophylaxis with low-molecular-weight heparin, however, we have no clear-cut parameters to refer to when deciding whether to administer prophylaxis or not and a significant number of patients are not given prophylaxis due to the risk of bleeding.

The aim of the present study was to assess the possible effect of different prophylactic strategies in the prevention of venous thrombosis in a large series of cirrhotic patients who underwent hepatic resection for HCC.

MATERIALS AND METHODS

The records of 229 consecutive patients with chronic liver disease who underwent hepatic resection due to the presence of HCC between January 1999 and December 2008 were retrospectively reviewed to ascertain whether there was any difference in the incidence of venous thromboembolic or hemorrhagic complications between those patients who received venous thrombosis prophylaxis and those who did not.

Table 1 Baseline characteristics of the study population (mean ± SD) *n* (%)

Variables	All patients (*n* = 229)	Group A (*n* = 157)	Group B (*n* = 72)	*P* value
Age (yr)	65.0 ± 9.3	65.0 ± 9.8	63.0 ± 9.5	0.080
Gender (M/F)	171 (74.7)/ 58 (25.3)	119 (76.0)/ 38 (24.0)	52 (72.0)/ 20 (28.0)	0.330
Etiology of cirrhosis				0.200
Hepatitis C	148 (64.6)	106 (67.0)	42 (58.3)	
Hepatitis B	37 (16.2)	21 (14.0)	16 (22.2)	
Hepatitis B + C	15 (6.6)	7 (5.0)	8 (11.1)	
Non-viral	29 (12.7)	23 (14.0)	6 (8.3)	
Child-Pugh score				0.005
A	218 (95.2)	154 (98.0)	64 (89.0)	
B	11 (4.8)	3 (2.0)	8 (11.0)	
C	0			
MELD score	8.8 ± 1.5	8.5 ± 1.2	9.3 ± 1.9	0.001
Platelet count (× 10^3)	139 ± 60	150 ± 60	115 ± 51	0.001
Esophageal varices	63 (28.0)	34 (22.0)	29 (40.3)	0.003

MELD: Model for end-stage liver disease.

All patients in the present series had the diagnosis of chronic liver disease confirmed by histology which was carried out on the resected specimen. Etiology of liver disease was predominantly viral (87.3% of cases) (Table 1).

Preoperative Child-Pugh-Turcotte score[7] and model for end-stage liver disease (MELD)[8] score were available for all patients; other parameters that were taken into account to determine the severity of portal hypertension were platelet count and presence of esophageal varices. Two hundred and eighteen patients (95.2%) had class A liver disease according to the Child-Pugh scoring system, while 11 (4.8%) had class B and none had class C disease; the mean MELD score of the patients was 8.8 ± 1.5.

Body mass index (BMI), diabetes mellitus and clinical history of cardiovascular disease were recorded as possible risk factors for thromboembolism. Type of surgical resection (minor when one or less and major when more than one hepatic segment was resected), duration of surgery, intraoperative transfusion of blood and fresh frozen plasma (FFP) were also recorded (Tables 2 and 3). Minor hepatic resection was carried out in 219 cases (95%), while major hepatic resection was performed in 10 cases (5%).

A protocol for general surgical procedures for the prevention of venous thrombosis using low-molecular-weight heparin prophylaxis was always observed in the period considered here. In the case of hepatic resection in cirrhotic patients the decision on whether to use prophylaxis was left to the judgment of the surgeon who performed the resection based on preoperative coagulation tests and intraoperative findings. For those patients

Table 2 Details of surgery performed in the two groups

Variables	All patients (*n* = 229)	Group A (*n* = 157)	Group B (*n* = 72)	*P* value
Type of resection *n* (%)				0.610
Minor	219 (95.0)	150 (95.5)	69 (95.8)	
Major	10 (5.0)	7 (4.5)	3 (4.2)	
Duration of surgery (mean ± SD)	266 ± 99	261 ± 106	275 ± 83	0.320
i.o. blood transfusion [mL, median (range)]	128.2 (0-1500)	124.7 (0-1500)	154.1 (0-1200)	0.346
i.o. FFP transfusion [mL, median (range)]	175.7 (0-1200)	139.5 (0-1200)	266.6 (0-1200)	0.003

i.o.: Intraoperative; FFP: Fresh frozen plasma.

who were administered anticoagulant prophylaxis, this consisted of nadroparin calcium 0.3 mL or enoxaparin sodium 0.4 mL subcutaneously, starting from the day of surgery and continued for at least 7 d or until the patient was actively ambulant.

Prophylaxis was stopped when hemorrhagic complications developed.

Independent of the use of low-molecular-weight heparin, all patients had mechanical prophylaxis by means of anti-embolism stockings.

Patient follow-up included evaluation at the outpatient clinic on days 7 and 30 and months 3, 6, 9 and 12 after discharge from the Hospital.

VTE was defined as the symptomatic or asymptomatic occurrence of deep vein thrombosis confirmed by Doppler ultrasonography or venography; pulmonary embolism was confirmed by helical computed tomography.

Hemorrhagic complications were defined as follows: (1) Blood loss from surgical drainage associated with a significant drop in hemoglobin levels (> 1.5 g/dL from the last control); (2) Intraabdominal fluid collection with density at CT compatible with blood of diameter > 3 cm; and (3) Bleeding from the upper or lower gastrointestinal tract.

The analysis of risk factors for VTE included the following parameters: (1) age; (2) sex; (3) etiology of chronic liver disease; (4) Child-Pugh score; (5) MELD score; (6) presence of esophageal varices; (7) platelet count; (8) BMI; (9) chronic heart disease; (10) diabetes; (11) extent of surgical resection (major when more than 1 hepatic segment was resected); (12) duration of surgery; (13) intraoperative requirement for blood or FFP transfusion; and (14) prophylaxis with low-molecular weight heparin.

Statistical analysis

Continuous variables are reported as mean ± SD or in median and range on the basis of parametric assumption; differences between subgroups were investigated with Levene's test for equality of variances and compared with the Student *t*-test or Mann-Whitney test as appropriate. Categorical variables were reported in a number of cases and prevalence and differences in subgroups were compared using the χ^2 test with Yates correction. Univariate logistic regression analysis was applied in order to investigate risk factors for thrombosis or hemorrhage. *P*-values less than 0.05 were considered statistically significant in all the analyses. Statistical analysis was performed using the SPSS for Windows package (Version 10.0).

Table 3 Specific risk factors for venous thromboembolism in the two groups *n* (%)

Variables	All patients (*n* = 229)	Group A (*n* = 157)	Group B (*n* = 72)	*P* value
BMI > 30 kg/m^2	36 (17.1)	26 (17.8)	10 (15.4)	0.410
Diabetes	47 (20.5)	33 (21.0)	14 (19.4)	0.460
Cardiovascular disease	56 (24.5)	43 (27.0)	13 (18.1)	0.080

BMI: Body mass index.

RESULTS

One hundred and fifty-seven of the 229 (68.5%) patients received antithromboembolic prophylaxis (Group A) while the remaining 72 (31.5%) patients did not (Group B). The proportion of patients who received prophylaxis significantly varied with time: prophylaxis was given to 48 of 99 (48.4%) patients in the period 1999-2003 and to 109 of 130 (83.8%) patients in the period 2004-2008 (*P* = 0.001).

There was no difference in age, gender and etiology of liver disease between the 2 groups, while patients in group B had higher Child-Pugh and MELD scores, lower platelet counts and a higher prevalence of esophageal varices (Table 1).

Extent and duration of the hepatic resection and intraoperative blood transfusions were similar in the 2 groups, while in group B there was a significantly higher requirement for intraoperative transfusion of FFP (Table 2). This latter finding might indicate a higher bleeding tendency observed by the surgeon in the operative field, which resulted in the administration of greater amounts of FFP.

As regards the specific risk factors for venous embolism that were considered, there was no difference between the 2 groups (Table 3).

Two cases (0.87%) of deep venous thrombosis were observed: these were one case of pulmonary embolism secondary to a deep vein thrombosis of the leg in a patient who was receiving prophylaxis and one case of total portal vein thrombosis in a patient who did not receive prophylaxis: this latter patient had a Child score of A6, a MELD score of 13 with a low platelet count (113.000/mL) an INR = 1.3 and no esophageal varices, and underwent wedge resection and died of hepatic failure. The incidence of VTE was therefore 1.38% in patients who did not receive prophylaxis and 0.63% in those patients who were treated with low-molecular-weight heparin (*P* = 0.530).

Six cases of hemorrhagic complications were observed (2.62%); 5 of these cases occurred in those 157

Table 4 Analysis of possible risk factors for venous thromboembolism

Variable	Exp (B)	95% CI	*P* value
Child-Pugh score (score A *vs* B)	0.004	0.00-15.32	0.906
MELD score	1.748	0.96-3.16	0.132
Type of resection (minor *vs* major)	0.004	0.00-17.52	0.914
Platelet count	0.990	0.99-1.00	0.776
Esophageal varices	0.001	0.00-18.22	0.525
BMI	0.001	0.00-11.45	0.687
Diabetes	0.001	0.00-12.45	0.631
Cardiovascular disease	0.001	0.00-19.31	0.570
Duration of surgery	0.997	0.98-1.01	0.720
i.o. blood transfusion (mL)	1.000	0.99-1.00	0.490
i.o. FFP transfusion (mL)	1.001	0.99-1.00	0.518
VTE prophylaxis	0.455	0.02-7.38	0.531

Table 5 Analysis of possible risk factors for hemorrhagic complications

Variable	Exp (B)	95% CI	*P* value
Child-Pugh score (score A *vs* B)	0.004	0.00-23.72	0.742
MELD score	1.280	0.83-1.95	0.252
Type of resection (minor *vs* major)	0.004	0.00-20.75	0.763
Platelet count	0.987	0.99-1.02	0.445
Esophageal varices	5.559	0.99-31.14	0.050
BMI	0.000	0.00-27.45	0.389
Diabetes	0.000	0.00-24.28	0.248
Cardiovascular disease	1.564	0.27-8.77	0.454
Duration of surgery	0.997	0.98-1.00	0.460
i.o. blood transfusion (mL)	1.001	0.99-1.00	0.315
i.o. FFP transfusion (mL)	1.002	0.98-1.00	0.073
VTE prophylaxis	0.443	0.26-20.42	0.387

VTE: Venous thromboembolism.

patients who received prophylaxis (prevalence: 3.18%) and one in patients who did not receive prophylaxis (prevalence: 1.38%); the difference was not significant ($P = 0.380$). The hemorrhagic complications consisted of prolonged blood leakage from the surgical drains requiring blood transfusion (3 cases), intraperitoneal blood collection (2 cases) and gastric bleeding (1 case). Only 1 of the above-mentioned cases required invasive intervention (CT-guided percutaneous drainage of intraperitoneal collection).

None of the considered risk factors proved to be significantly associated with VTE in the univariate analysis, and only the presence of esophageal varices was linked to an increased risk of hemorrhagic complications (Tables 4 and 5).

DISCUSSION

Despite the clinical relevance of this topic, to our knowledge no reports have been published to date on the use of venous thrombosis prophylaxis in cirrhotic patients undergoing hepatic resection for HCC. The absence of clear guidelines for prophylaxis of thromboembolism in the specific setting of hepatic surgery in patients such as those with chronic liver disease who are known to have imbalances in coagulative function may induce those surgeons with less experience in hepatobiliary surgery to avoid prophylaxis for fear of hemorrhagic complications; on the other hand, administering prophylaxis to patients with severe coagulative impairment and severe portal hypertension possibly following an extensive liver resection should be done on more solid grounds than simple adherence to existing guidelines that were drawn up for open abdominal surgery. In both cases, should thromboembolic or hemorrhagic complications develop, then the possibility of a malpractice accusation would be consistent[9].

In our experience, we found a particularly low incidence of deep vein thrombosis in cirrhotic patients who underwent liver resection, which could be partially justified by the absence of specific postoperative screening; however, at our center, HCC patients are always closely monitored with follow-up after resection and we can therefore exclude the fact that major thrombotic complications took place after hospital discharge which do not show up in the clinical records. Of note, all the patients in this report received prophylaxis with a mechanical method (anti-embolism stockings) which, together with the peculiarities of the study population, may have played a role in keeping the rate of VTE particularly low.

Hemorrhagic complications after liver resection are often poorly defined in specific reports, and the impression is that only those that require invasive maneuvers are usually reported; nevertheless, the incidence of these complications after resection in cirrhotic patients ranges between 1% and 8%[5,10,11]. The hemorrhagic complications reported in the present study were mainly represented by prolonged blood leakage from the surgical drains requiring blood transfusion. Although a trend towards a higher incidence of hemorrhage following resection was observed in those patients who received prophylaxis, the difference between the 2 groups was not significant.

Prophylaxis was withheld mainly in those patients who had a higher Child-Pugh or MELD score, lower platelet count and higher prevalence of esophageal varices; however, the overall increase in prophylaxis administration over time reflects an increase in confidence in handling it.

The surgeon performing the hepatic resection can assess some elements such as the bleeding tendency observed in the operative field and the degree of portal hypertension as revealed by the number and size of hepatofugal collateral veins, which can provide information that goes beyond what can be assessed with laboratory and imaging screening. However, the categorization of these elements largely depends on the degree of experience and confidence of the surgeon, and their effective relationship with the risk of bleeding in the postoperative period is difficult to demonstrate.

Similarly, in the cirrhotic patient, the common coagulative tests such as prothrombin time or INR poorly predict the effective risk of bleeding: in fact, these tests

only measure the activity of procoagulant factors while they ignore possible changes in the activity of anticoagulant factors that, in liver disease, are also deficient[12].

In our study, a greater amount of FFP was administered to those patients who did not receive prophylaxis, which might reflect a bleeding tendency that was observed at surgery. We believe that, unless clear guidelines are validated by large clinical trials, antithromboembolic prophylaxis should probably be avoided in those patients who are judged at high risk of bleeding by the surgeon.

Despite their low incidence in this series, the thromboembolic complications seen after surgery were life-threatening, however, we did not experience similar serious hemorrhagic complications. In the absence of more reliable tools to quantify the probability of bleeding it seems reasonable to avoid prophylaxis when portal hypertension is present or significant bleeding is observed at surgery.

Further prospective studies are necessary to establish guidelines for application in this specific setting.

COMMENTS

Background

Hepatocellular carcinoma (HCC) is the most common primary neoplasm of the liver and often arises in the context of a chronic liver disease that impairs coagulative function. Surgical resection is the best option to cure HCC, however, surgery on cirrhotic liver may increase the risk of bleeding. Despite the clinical relevance of the matter, no guidelines are available on the administration of antithromboembolic prophylaxis in cirrhotic patients undergoing hepatic resection.

Innovations and breakthroughs

The study shows that the risk of venous thromboembolism after hepatic resection in cirrhotic patients is low. A trend towards an increased incidence of postoperative hemorrhage was observed in patients who received prophylaxis. Portal hypertension, as demonstrated by the presence of esophageal varices, is significantly associated with the risk of bleeding.

Applications

The absence of guidelines for prophylaxis of thromboembolism specifically aimed at patients with chronic liver disease undergoing hepatic surgery can lead to the generalized application of prophylactic schemes which are used in the setting of open abdominal surgery, thus increasing the risk of bleeding. Conversely, to withold prophylaxis might increase the risk of thromboembolism. Both these policies can be dangerous and lead to malpractise accusations. Prospective studies are necessary to establish specific guidelines.

Peer review

This is a good manuscript to get published but needs some more information. The manuscript is well written and would be helpful in the field of hepatic surgery.

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