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Prevention of venous thromboembolism after resection of primary liver cancer with low molecular weight heparin and its association with P-selectin, lysosomal granule glycoprotein, platelet activating factor and plasma D-dimer

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Abstract. – OBJECTIVE: We aimed at analyzing the efficacy of low molecular heparin in the prevention of venous thromboembolism (VTE) after resection of primary liver cancer and at exploring the correlation of VTE with P-selectin (CD62P), lysosomal granule glycoprotein (CD63), platelet activating factor (PAF) and plasma D-dimer (D-D).

PATIENTS AND METHODS: A total of 233 patients treated with primary liver cancer resection in our hospital from February 2014 to October 2016 were enrolled in this study. The patients were randomly divided into the observation group (n=117) and the control group (n=116). The observation group received a subcutaneous injection of low molecular weight heparin at 2-7 days after surgery, and the control group was not treated with anticoagulation. The prevalence of VTE and the changes of CD62P, CD63, PAF, and D-D before and after treatment were compared between the two groups. The VTE prevalence after surgery, the changes of CD62P, CD63, PAF, D-D before and after surgery and the correlation of the above indexes with VTE were analyzed.

RESULTS: The prevalence of VTE in the observation group was 0.85% (1/117), which was lower than that of the control group (13.79%) (16/116); the difference was statistically significant ($p<0.05$). There was no significant difference in blood coagulation function between the two groups before and after operation ($p>0.05$). The CD62P, CD63, PAF, and D-D of the two groups were continuously decreased after the operation, and the serum CD62P, CD63 and plasma D-D of the observation group 6 d and 10 d after operation were lower than that of the control group; the difference was statistically significant ($p<0.05$). The serum CD62P, CD63 and plasma D-D in the VTE group 6 d and 10 d after operation were lower than those in the non-VTE group; the differences were statistically significant ($p<0.05$).

CONCLUSIONS: Low molecular weight heparin can effectively prevent VTE after primary liver cancer resection. Regularly monitoring CD62P, CD63, PAF, and D-D in patients after the operation is pivotal for early diagnosis, evaluation and treatment of VTE.

Key Words
Low molecular weight heparin, Primary liver cancer, Venous thrombosis, P-selectin, lysosomal granule glycoprotein, Platelet activating factor, D-dimer.

Introduction

Venous thromboembolism (VTE) includes deep venous thrombosis, pulmonary thromboembolism and mesenteric venous thrombosis, which are common complications after surgery[1-3]. The mechanism is related to the injured venous wall, hypercoagulable state and decreased blood flow rate[4,5]. Previous reports[6-8] have shown that the prevalence of VTE after general surgery is about 10-40%, and the prevalence of VTE after resection of primary liver cancer is higher than the average. The occurrence rate of lethal VTE is as high as 5%. The mechanism is related to procoagulant factor imbalance induced acquired procoagulant state in liver cancer patients[9,10]. However, the application of low molecular weight heparin for anticoagulation in primary liver cancer patients

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after resection has been controversial[11-14]. In this study, the prevention of venous thromboembolism after resection of primary liver cancer with low molecular weight heparin was prospectively analyzed. Furthermore, the mechanism of VTE was investigated to provide a reference point for the prevention, evaluation and treatment of VTE.

Patients and Methods

Patients

A total of 233 patients treated with primary liver cancer resection in our hospital from February 2014 to October 2016 were enrolled in this study for prospective study. The patients were randomly divided into the observation group (n=117) and the control group (n=116) according to the random table method. The baseline materials, which included age, gender, liver function Child-Pugh grade and preoperative coagulation function, were not statistically different (p>0.05); thus, they were comparable (Table I). This clinical study was approved by the Ethics Committee of our hospital. All the patients or their relatives signed the informed consent.

Inclusion and Exclusion Data

Inclusion data: 1- the primary liver cancer was confirmed by histopathological examination; 2- the patients were conformed to the indication for liver cancer resection, and the Child-Pugh grade was grade A or grade B; 3- platelet count >80×10^9/L, the coagulation function was normal. Exclusion criteria: 1- there was hematological disease or thrombotic disease; 2- the intraoperative blood loss was more than 1000 mL and the operation time > 5 h; 3- there was regular administration of anticoagulant drug or thrombolytic drug.

Methods

Anticoagulant Regimen

The patients in both groups received primary liver cancer resection. The observation group received subcutaneous injection of low molecular weight heparin calcium on 2nd-7th day after operation (Hainan Unipul Pharmaceutical Co., Ltd., Haikou, China, specifications: 1 mL: 5000 U), 5000 U every time once per day; the control group didn't receive any anticoagulant therapy. The patients in both groups were asked to do lower limb activity on the bed and to do out-of-bed activity as early as possible.

Calculation of VTE Prevalence

VTE was diagnosed based on the examinations including color Doppler ultrasound, enhanced CT and CTV combining with the clinical manifestations involving: postoperative lower limb swelling, soreness, walking pain, chest pain, chest stuffiness, sudden decreased oxygen saturation after activity, hemoptysis, abdominal distension, abdominal pain, no anal aerofluxus for a long time, early-stage postoperative intestinal obstruction manifestation and peritonitis. The case number of VTE was recorded to calculate prevalence of VTE.

Detection of Indexes

After operation, the coagulation factors including prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR), were detected. Plasma P-selectin (CD62P), lysosomal granule glycoproteins (CD63), platelet activating factor (PAF), and plasma D-dimer (D-D) before the operation, on 6th and 10th day after operation, were detected. All the detection methods were based on Aerts et al[15] and Nettis et al[16] findings.

Table I. Comparison of baseline clinical data between two groups (n/%).

Index		Observation group (n=117)	Control group (n=116)	p-value
Age (year)		58.52±8.71	57.69±8.38	> 0.05
Preoperative coagulation function	PT (s)	12.65±1.13	12.57±1.08	> 0.05
	APTT (s)	30.26±2.75	30.41±3.50	> 0.05
	INR	2.46±0.44	2.65±0.39	> 0.05
Gender	Male	91 (77.78)	85 (73.28)	> 0.05
	Female	26 (22.22)	31 (26.72)	
Child-Pugh grade	Grade A	94 (80.34)	91 (78.45)	> 0.05
	Grade B	23 (19.66)	25 (21.55)	

Note: PT: prothrombin time; APTT: activated partial thromboplastin time; INR: in-ternational normalized ratio.

Table II. Comparison of coagulation function between two groups ($\bar{x} \pm s$).

Index	Observation group (n=117)		Control group (n=116)	
	Before operation	After operation	Before operation	After operation
PT (s)	12.65±1.13	13.18±0.71	12.57±1.08	13.02±1.14
APTT (s)	30.26±2.75	32.56±2.40	30.41±3.50	31.05±3.42
INR	2.46±0.44	2.62±0.58	2.65±0.39	2.47±0.66

Note: *p<0.05 compared before operation within the same group; #p<0.05 compared with the control group at the same time point.

Besides, the patients were divided into VTE and non-VTE group based on whether they had VTE. The perioperative serum CD62P, CD63, PAF and plasma D-D were compared between two groups to explore the correlation of above indexes with VTE prevalence.

Statistical Analysis

SPSS 18.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the clinical data. The enumeration data were presented as (n/%) and analyzed by χ^2-test, the measurement data were presented as ($\bar{x} \pm s$) and analyzed by t-test. p<0.05 was considered as statistically significant.

Results

VTE Occurrence Rate

The prevalence of VTE in the observation group was 0.85% (1/117), which was lower than that of the control group (13.79%) (16/116); thus, the difference was statistically significant (p<0.05).

Change of Coagulation Function

There was no significant difference in blood coagulation function between the two groups before and after operation (p>0.05) (Table II).

Change of Other Indexes

CD62P, CD63, PAF and D-D of the two groups were continuously decreased after the operation, and the serum CD62P, CD63 and plasma D-D of the observation group 6 d and 10 d after operation were lower than that of the control group. The differences were statistically significant (p<0.05) (Table III).

Correlation of the Indexes with VTE Prevalence

The serum CD62P, CD63 and plasma D-D in the VTE group at 6 d and 10 d after operation were lower than those in the non-VTE group; the differences were statistically significant (p<0.05) (Table IV).

Discussion

VTE is a common and severe complication emerging after operation, among which deep venous thrombosis and pulmonary thromboembolism can directly threaten to the life of patients[17,18]. A higher number of researches[19-21] believe that besides personal reasons – including age, gender, underlying disease and malignant tumor, the intraoperative and postoperative long-term bed rest induced slow venous return rate, intraoperative local tissue injury induced vascular endothelial cell hypoxic swelling and postoperative stress state

Table III. Comparison of other indexes between two groups ($\bar{x} \pm s$).

Index	Observation group (n=117)			Control group (n=116)		
	Before operation	6 d after operation	10 d after operation	Before operation	6 d after operation	10 d after operation
CD62P (%)	61.33±8.26	44.27±7.71*	19.76±3.08*	60.85±8.33	54.33±7.65*#	38.17±6.24*#
CD63 (%)	37.51±5.74	23.61±5.24*	19.70±3.41*	38.51±5.49	25.90±4.58*#	18.63±3.22*#
PAF (pg/mL)	352.67±19.40	280.44±18.56*	195.71±15.33*	360.17±18.89	291.47±16.58*	204.37±15.57*
D-D (μmol/L)	3.92±0.33	2.50±0.31*	1.52±0.24*	3.95±0.34	3.11±0.26*#	2.08±0.37*#

Note: *p<0.05 compared with before operation within the same group; #p<0.05 compared with the control group at the same time point.

Table IV. Comparison of the indexes between VTE group and non-VTE group ($\bar{x}$±s).

Index	VTE group (n=17)			Control group (n=216)		
	Before operation	6 d after operation	10 d after operation	Before operation	6 d after operation	10 d after operation
CCD62P (%)	61.29±8.44	57.81±7.32*	40.72±7.59*	59.87±8.26	40.15±7.26*#	16.43±3.52*#
CD63 (%)	37.38±5.26	26.44±4.37*	20.41±3.76*	39.04±5.81	19.81±5.30*#	16.99±3.55*#
PAF (pg/mL)	355.81±19.95	275.47±14.85*	208.46±17.09*	362.44±17.51	264.57±19.02*	196.24±16.08*
D-D (μmol/L)	3.97±0.34	3.24±0.35*	2.35±0.40*	3.88±0.36	2.24±0.39*#	1.37±0.11*#

Note: *p<0.05 compared before operation within the same group; #p<0.05 compared with the control group at the same time point.

– are also important reasons of enhanced platelet aggregation function and decreased fibrinolytic function, further inducing VTE prevalence. Previous studies have shown that primary liver cancer is usually complicated with different degrees of liver cirrhosis. Those patients are in a long-term hypocoagulation state and have spontaneous anti-coagulation effect[22-24]. However, the latest researches have shown that liver cirrhosis can promote the procoagulation and anticoagulation factors synthesized by liver to reach a new balance point. This balance is very unstable: on one hand, the reduction of the procoagulation factors, including coagulation factors II, V, VII, X, XI, XII and fibrinogen, can increase the bleeding risk significantly; on the other hand, the reduction of anticoagulation factors, including antithrombin, protein C, protein S and plasminogen, can increase procoagulation risk and increase VTE prevalence[25,26]. However, it is still controversial about the prevention of VTE after primary liver cancer resection. Researches[27-29] show that heparin can decrease the occurrence rates of bacteria translocation and dyspnea without increasing the bleeding risk, and prevent VTE prevalence. However, in the clinical practice the preventive anticoagulation therapy has not been widely applied due to the bleeding risk[30-32].

In this study, the effect of low molecular weight heparin in preventing VTE after resection of primary liver cancer was prospectively analyzed. The results showed that low molecular weight heparin has no significant effect on postoperative coagulation function, which not only verifies the previous conclusion but also suggests that a proper dosage of low molecular weight heparin does not increase the bleeding risk. In the comparison of VTE prevalence, we found that low molecular weight heparin application for 6 days could effectively control the VTE risk. The occurrence rate of VTE in the observation group was only 1/16 of that in the control group that did not receive anticoagulation treatment. The advantages are as follows: although the surgical incision of primary liver cancer resection is exposed extensively, there is much resected tissue and the postoperative residue cavity is big, low molecular weight heparin doesn't cause significant adverse effect on the coagulation function of patients, thus avoiding bleeding and preventing VTE prevalence.

To further confirm the mechanism of low molecular weight heparin and the indexes to evaluate VTE risk, we selected CD62P, CD63, PAF and D-D to analyze their correlation with VTE. The results showed that the application of low molecular weight heparin accelerated the decreasing rate of CD62P, CD63 and plasma D-D in the observation group. The decrease in CD62P suggests the inhibition of platelet activation reaction[33,34], whilst the decrease of CD63 suggests that the platelet activation and damage are under control[35,36]. Next, the decrease of D-D suggests that the hypercoagulable state and hyperfibrinolysis state are significantly improved[37,38]. Due to the above changes, the VTE prevalence in the observation group was significantly decreased. Furthermore, PAF is synergistic with CD62P to mediate the adhesion of leukocytes and vascular endothelial cell, active leukocytes, promoting the expression of integrins. However, PAF was not statistically different between observation group and control group at the same time point. There was also no difference of PAF between VTE group and non-VTE group, suggesting that the effect of low molecular weight heparin on serum PAF expression is not significant during the prevalence and development of VTE, accordingly to previous studies[39-41].

Conclusions

We showed that the low molecular weight heparin can effectively prevent VTE after primary liver cancer resection, the mechanism of which may be related to the down-regulation of CD62P,

CD63 and D-D by low molecular weight heparin. In the future practice, dynamically monitoring the perioperative serum CD62P, CD63, PAF and plasma D-D in patients will be pivotal for evaluating VTE risk, early intervention, prevention and treatment of VTE.

Conflict of Interest

There is no conflict of interests.

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