Clinical observation of the efficacy of low-molecular-weight heparin calcium in prophylaxis of the deep venous thrombosis following the gynecological tumor surgery

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Abstract: Present study is conducted to investigate the efficacy and safety of application of low-molecular-weight heparin calcium in the prophylaxis of deep venous thrombosis (DVT) following the laparoscopic surgery for gynecological tumors, so as to provide reference for the selection of anti-coagulant procedure in clinical practice. A total of 180 patients who underwent the laparoscopic surgery for the gynecological tumors in this hospital between January 2015 and December 2017 were enrolled in this study, and according to the anti-coagulant procedure, they were divided into two groups, i.e. the control group and the observation group, with 90 patients in each group. In the control group, 90 patients were free from the anti-coagulant agent or drugs affecting the coagulant functions, while those in the observation group received the subcutaneous injection of low-molecular-weight heparin calcium for consecutive 5 days. Then we compared the serological indicators, prothrombin time (PT), cross-section diameter of the lower limb, hemodynamic indicator and the incidence rate of complications. Following postoperative 5 days, the levels of fibrinogen and D-dimer in the observation group were (2.66±0.72) g/L and (0.61±0.17) μg/mL, significantly lower than those in the control group, and the differences had statistical significance (t=4.667, P=0.019; t=3.967, P= 0.029). At 3 d and 5 d after operation, PTs in the observation group were (13.74±3.92) s and (13.84±3.13) s, also superior to the control group (t=3.031, *P*=0.042; t=3.553, P =0.034). In the observation group, the cross-section diameter of lower limb and blood flow rate were (20.22±3.51) cm and (0.93±0.17) m/s, respectively, which were better than the control group, and the difference had statistical significance (t=4.412, P=0.021; t =4.724, P=0.019). In the observation group, the incidence rate of complications was only 3.33%, significantly lower than 10.00% in the control group (c^2 =6.158, P=0.004). The application of the low-molecular-weight heparin calcium for anti-coagulation in the prophylaxis of the DVT following the laparoscopic surgery of gynecological tumor can better ameliorate the hemodynamics of patients, and prevent the formation of DVT.

Keywords: Low-molecular-weight heparin calcium, anti-coagulation, gynecological tumor, DVT, safety.

INTRODUCTION

Clinically, the deep venous thrombosis is frequently seen and mainly occurs in the patients with trauma in lower limbs or following the surgery of tumors, in which the decreased viscosity contributes to an increase in coagulability of blood, further leading to the coagulation of platelet to block the vessels, and enlarging the thrombus and occluding the vessels (Xie Hua *et al*., 2011). Relevant literatures suggest that the incidence rate of the venous thrombus following the surgery for gynecological tumors is 10% to 30%, among which the benign DVT occupies only 1% to 15%, but the malignant DVT takes up about 19.8% to 30%. Due to the bladder lithotomy position and the suppression on the pelvic vessels posed by intra-abdominal pressure, the resistance of venous return of the lower limbs is increased, together with an increase in the risk of the DVT, severely affecting the prognosis and life quality of patients (Xia *et al*., 2012; Li *et al*., 2011), or even inducing the pulmonary thrombosis or death. Thus, in-time diagnosis of DVT and appropriate treatment are quite important for the patients who underwent the surgery for gynecological tumors. Prophylaxis for the venous thrombus mainly includes the mechanical (stretch socks) and medication strategies (low-molecular-weight heparin calcium) (Zhang *et al*., 2009). Hence, anti-coagulant therapy is regarded as a key link in recovery of patients from the laparoscopic surgery for gynecological tumors. In this study, a total of 180 patients who underwent the laparoscopic surgery for the gynecological tumors received the different anti-coagulant therapies, so as to explore the efficacy and safety of the application of low-molecular-weight heparin calcium in the prophylaxis of deep venous thrombosis (DVT) following the laparoscopic surgery for gynecological tumors, thereby providing reference for the selection of anti-coagulant procedure in clinical practice.

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MATERIALS AND METHODS

Clinical data

A total of 180 patients who underwent laparoscopic surgery for the gynecological tumors in this hospital between January 2015 and December 2017 were divided into the control group and the observation group according to the anti-coagulant therapies, with 90 patients in each group. In the control group, the age of patients ranged from 40 to 69 years old, with an average of (46.77±6.42) years old; there were 79 patients with uterine fibroid, 8 with endometrial cancer (TNM I) and 13 with cervical cancer (TNM I). In the observation group, the age of patients ranged from 41 to 71 years old, with an average of (47.42±6.93) years old; there were 76 patients with uterine fibroid, 7 with endometrial cancer (TNM I) and 17 with cervical cancer (TNM I). Comparison of the baseline data (age, tumor types, etc.) between two groups showed that differences had no statistical significance ($p>0.05$).

Enrollment criteria

a) Patients who were confirmed with the gynecological tumors through the imaging examination and pathological examination before surgery; b) patients with no hypercoagulability; c) patients with no evident anomaly in functions of liver, kidney, heart or lung; d) patients with no allergy to the anti-platelet drugs or heparin; e) patients with no thrombus-related diseases in preoperative examination; f) patients who or whose family had signed the informed consents; g) this study had been approved by the Ethic Committee of the hospital.

Treatment

All patients underwent the laparoscopic total hysterectomy, among which patients with malignant tumors received the bilateral salping-oophenrectomy, extensive uterine resection and the pelvic lymph node dissection. In the control group, patients were free from the anti-coagulant drugs, or drugs affecting the coagulant functions. In the following day, anti-coagulant therapy was carried out using the low-molecular-weight heparin calcium (0.4mL; GlaxoSmithKline, SFDA No. J20090004) once per day for consecutive 5 days. Following the surgery, we monitored the coagulation-related indexes and observed the clinical symptoms of patients in two groups. For any related symptoms, color ultrasonic examination was performed to identify the thrombus.

Observation indexes

a) Serological indexes: fibrinogen and D-dimer; b) prothrombin time (PT); c) the cross-section diameter of lower limb; d) blood flow rate through the color ultrasonic examination; e) preoperative complications.

STATISTICAL ANALYSIS

SPSS 21.0 software was applied to process the data. Measurement data were analyzed using *t* test or chi-square test, while the enumeration data using the chi-square test. $p<0.05$ suggested that the difference had statistical significance.

RESULTS

Serological indicators

Following postoperative 5 days, the levels of fibrinogen and D-dimer in the observation group were significantly lower than those in the control group, and the differences had statistical significance ($p<0.05$). The intragroup comparison of the fibrinogen and D-dimer in the control group showed that the differences had statistical significance (t=4.667, $p=0.019$; t =3.967, $p=0.029$; table 1).

PT in two groups

At 3 d and 5 d after operation, PTs in the observation group were also superior to the control group ($p<0.05$); at different time points before and after treatment, intragroup comparisons of the PT in the control group and the observation group showed that the differences had statistical significance (t=3.031, $p=0.042$; t=3.553, $p=0.034$; table 2).

The cross-section diameter and blood flow rate of the lower limbs of patients

Before treatment, comparisons of the cross-section diameter and blood flow rate of the lower limbs of patients between two groups showed that the differences had no statistical significance ($p>0.05$). In the observation group, the cross-section diameter of lower limb and blood flow rate were better than the control group, and the difference had statistical significance ($p<0.05$; table 3).

Complications in two groups

In the observation group, there was 1 patient with ecchymosis and 2 with local hematoma (active bleeding according to the ultrasonic examination); in the control group, there were 9 patients with DVT, among which there were 3 patients with femoral venous thrombus, 2 with iliac venous thrombus and 2 with muscular veniplex thrombosis of calf. In the observation group, the incidence rate of complications was only 3.33% (3/90), significantly lower than 10.00% (9/90) in the control group ($c^2=4.031$, P=0.045).

DISCUSSION

DVT secondary to the laparoscopic surgery for the gynecological tumors may be induced by various causes: a) The blood of patients with malignant tumors is highly coagulant: The degradation of malignant tumors can induce an increase in the platelet and the blood coagulation factor, and the proteins relating to the inhibition of fibrinolysis that are secreted and expressed in the malignant tumor cells can facilitate the thrombosis.

Table 1: Comparison of the serological indicators of patients in two groups after the surgery

Group	Case (n)	Fibrinogen (g/L)			D-dimer (μg/mL)		
		Before surgery	Postoperative 3 d	Postoperative 5 d	Before surgery	Postoperative 3 d	Postoperative 5 d
Control group	90	2.46±0.75	2.76±0.83	3.83±1.01	0.57±0.13	0.58±0.17	0.76±0.20
Observation group	90	2.50±0.71	2.65±0.63	2.66±0.72	0.58±0.14	0.59±0.16	0.61±0.17
t		0.383	1.043	9.329	0.489	0.405	5.424
p		0.703	0.298	<0.0001	0.626	0.687	<0.0001

Table 2: Comparison of the PT of patients in two groups (s)

Group	Case (n)	Before surgery	Postoperative 3 d	Postoperative 5 d	F value	*P value*
Control group	90	12.48±2.52	10.84±3.13	10.64±2.93	12.28	<0.0001
Observation group	90	12.66±2.71	13.74±3.92	13.84±3.13	3.93	0.021
t		0.486	5.766	7.44		
p		0.629	<0.0001	<0.0001		

Table 3: Comparison of the cross-section diameter and blood flow rate of the lower limbs of patients between two groups

Group	Case (n)	Time	Cross-section diameter (cm)	Blood flow rate (m/s)
Observation group	90	Before treatment	19.53±2.28	1.11±0.20
		After treatment	20.22±3.51[a]	0.93±0.17[a]
Control group	90	Before treatment	20.04±2.63	1.08±0.17
		After treatment	25.72±4.16	0.62±0.10

b) During the surgery for tumors, the content of protein fiber in the blood is evidently augmented, resulting in an acute increase of viscosity of blood. c) The relatively long surgical time, during which patients are required to keep in a position for a long time, leads to the blocked blood circulation. d) Thrombosis is more susceptible due to the condense pelvic veins, thin venous wall, lack of support, slow blood flow and the intra- or postoperative dysfunction in pelvic venous return. e) Massive intraoperative bleeding amount and dehydration contribute to an increase in the viscosity of blood, which in turn leads to an elevation in the incidence rate of venous thrombus. f) After surgery, the administration of hemostatics and long bedridden time may severe suppress the lower limbs of patients, and slow the blood flow (Liu *et al*., 2013; Patterson *et al*., 2011).

Following the surgery for gynecological tumors, damaged vessels, hypercoagulative blood and the slow blood flow rate contribute to the abnormal coagulation in the deep venous cavity to impede the venous blood and affect the postoperative recovery of patients, as well as the life quality of patients. Thus, anti-coagulant treatment is quite important for prophylaxis of the thrombosis (Yin *et al*., 2011; Van *et al*., 2012). Besides, application of fibrous protein for thrombolysis and prophylaxis of the thrombus is the major link in postoperative treatment of gynecological tumors.

Following the anti-coagulation treatment using low-molecular-weight heparin calcium, the anti-Xa activity of patients is increased, which is correlated mainly with the anti-coagulant mechanism (Liu *et al*., 2010). Low-molecular-weight heparin, a fragment obtained from the heparin, can selectively suppress the Xa activity during anti-coagulation. Thus, the roles of low-molecular-weight heparin against the thrombus and bleeding are independent, which suggest that the application of low-molecular-weight heparin cannot only guarantee the anti-thrombosis effect, but also control the bleeding risk (Hsin *et al*., 2012. Zhang Yong *et al*., 2014). Simultaneously, administration of low-molecular-weight heparin can promote the release of the activator of tissue fibrinoclase for fibrinolysis, plus the mediating effect of the endothelial cells, to activate the plasminogen in vascular endothelium and tissues (Pregowski *et al*., 2011), thereby transforming into the fibrinolysin to promote the fibrinolytic effect and protect the vascular endothelium to enhance the anti-thrombosis effect. The results of this study also indicated that the index of fibrinogen of patients in the observation group was superior to that in the control group. Additionally, we also identified that APTT and PT in the observation group were somehow ameliorated before the operation, suggesting that the low-molecular-weight heparin calcium suppressed the platelet coagulation and prevent the migration of thrombus to the deep veins, thus averting the occurrence of the DVT. However, due to the lack of active anti-coagulant treatment, hypercoagulability remained following the operation, which contributes to a higher incidence rate of DVT than the observation group. Those who received the

surgery for gynecological tumors are frequently aged patients, with hypercoagulability, which, plus the general anesthesia and the suppression on the veins in lower limbs due to the lymph node dissection, results in the susceptibility to the thrombosis due to the slowed blood flow rate. Meanwhile, during the laparoscopic surgery, CO_2-induced pneumoperitoneum pressure is almost 3 to 5 times that of the regular pressure on the veins in lower limbs, and the increased inner pressure results in the augmented blood pressure, while the slowed blood flow aggravates the thrombosis (Ding *et al*., 2014; Emmanuel *et al*., 2011).

In this study, we found that following the anti-coagulant treatment using low-molecular-weight heparin calcium, the indexes of patients in the observation group, including the cross-section diameter of lower limb and the blood flow rate, were all better than those in the control group, suggesting that low-molecular-weight heparin can effectively improve the hypercoagulability of blood and prevent the thrombosis. The serological indexes, including the fibrinogen and D-dimer, in the observation group were all lower than those in the control group. In light of the positive correlation between the fibrinogen and the whole blood viscosity, plasma viscosity, erythrocyte sedimentation rate and platelet coagulation, the lower levels of indexes in the observation group suggest that the application of low-molecular-weight heparin calcium can better control the levels of whole blood viscosity, erythrocyte sedimentation rate and platelet coagulation to avert the hypercoagulability of blood and the thrombosis. D-dimer is a kind of specific degradation product that is generated by the fibrinolysis of the cross linked fibrin monomers and serves as a specific indicator of fibrinolysis. In the observation group, the level of D-dimer was lower in the observation group, revealing that the degradation process of fibrinogen is under control, with a significant prophylactic effect on the thrombosis and improvement in the hemodynamic manifestations. Besides, the faster blood flow rate in the observation group suggested the better prophylactic effect on thrombosis.

CONCLUSION

Overall, the application of the low-molecular-weight heparin calcium for anti-coagulation in the prophylaxis of the DVT following the laparoscopic surgery of gynecological tumor can better ameliorate the hemodynamics of patients, and prevent the DVT. Thus, it is worthy of being promoted in clinical practice.

REFERENCES

Ding Guannan, Li Shuren and Pan Zhenxiang *et al* (2014). Effects of batroxobin on perioperative blood loss and coagulation in patients with low molecular weight heparin when undergoing the total hip replacement. *Chin. J. Epidemiol.,* **36**(06): 737-740.

Emmanuel Addo Yobo, Dang D Anh, Hesham F El Sayed *et al* (2011). Outpatient treatment of children with severe pneumonia with oral amoxicillin in four countries: The MASS study. *Tropical Med. Int. Health,* **16**(8): 1127-1129.

Hsin Hung Cheng, Guan Ying Tseng, Hsiao Bai Yang*et al* (2012). Increased numbers of Foxp 3 positive regulatory T cells in gastritis, peptic ulcer and gastric adenocarcinoma. *World J. Gastroenterol.,* **18**(1): 34-43.

Li Yan, Huang Huaiyu and Gu Chengzhi *et al* (2011). Effect of intermittent administration of low molecular weight heparin (lmwh) on carotidartery plaque and serum inflammatory biomarkers in patients with cerebral infarction. *J. Radioimmunol.,* **24**(06): 670-672.

Liu Guoqing (2010). Study the Effect of low molecular weight heparins combined with shuxuening injection in the treatment of cerebral infarction accompanied with carotid atherosclerosis. *Hebei Medicine,* **16**(10): 1166-1169.

Liu Qi, Cheng Yuexin and Ni Leng *et al* (2013). Clinical observation of neutralizing heparin with protamine in carotid endoarterecomy. National. *Med. J. China,* **93**(33): 2650-2653.

Patterson SM, Hughes CM and Cardwell C *et al* (2011). A cluster randomized controlled trial of an adapted U.S. model of pharmaceutical care for nursing home residents in Northern Ireland (Fleetwood Northern Ireland study): A cost-effectiveness analysis. *J. Am. Geriatrics Society,* **59**(4): 1102-1105.

Pregowski J, Kepka C and Kalinczuk L *et al* (2011). Comparison of intravascular ultrasound quantitative coronary angiography and dual source 64 slice computed tomography in the preprocedural assessment of significant saphenous vein graft lesions. *Am. J. Cardiol.,* **107**(10): 1453-1459.

VanNess PH, Peduzzi PN and Quagliarello VJ (2012). Efficacy and effectiveness as aspects of cluster randomized trials with nursing home residents: Methodological insights from a pneumonia prevention trial. *Contemporary Clinical Trials,* **33**(6): 2320-2324.

Xia Wu, Xuebin Zhang and Jie Zhu *et al* (2012). Caesarean scar pregnancy: Comparative efficacy and safety of treatment by uterine artery chemoembolization and systemic methotrexate injection. *Eur. J. Obstet. Gynecol. Reproductive Biol.,* **161**(1): 75-79.

Xie Hua, Lin Hongli and Chen Shuni *et al* (2011). Comparison of anticoagulation using regional heparin， heparin free and low molecular weight heparins in hemodialysis patients with high risk of bleeding. *J. Dalian. Medical University,* **33**(1): 46-49.

Yin Changsen, Hu Liqun and Rong Rong (2011). The study of TOAST classification in ischemic stroke and the research on vulnerable carotid artery plaque in

elderly cadre. *Chin. J. Clin. Healthcare*, **14**(05): 466-468.

Zhang Xiaoqing, He Yun and Ding Min *et al* (2009). Simultaneous determination of tryptophan and kynurenine in plasma samples of children patients with Kawasaki disease by high-performance liquid chromatography with programmed wavelength ultraviolet detection. *J. Chromatography*, **877**(16/17): 1678-1682.

Zhang Yong, Wang Chen and Wang Jun *et al* (2014). A comparative study of domestic bivalirudin and ordinary heparin during emergency percutaneous coronary intervention. *Chin. J. Cardiovascular Med.*, **19**(02): 115-117.