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Original Article

Prophylactics for lower-extremity deep venous thrombosis in high-risk patients after gynecologic surgery: a prospective study

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Abstract: Objective: This study aimed to investigate the effect of prophylactics on lower-extremity deep venous thrombosis (LEDVT) in high-risk patients after gynecologic surgery. Method: A total of 690 patients with a high risk of deep venous thrombosis (DVT) were included. The patients were divided into four groups by envelope method. Graduated compression stockings (GCS) were used as a basic prophylactic for DVT in the control group, while advanced prophylactics, such as GCS + low-molecular-weight heparin (LMWH), GCS + intermittent pneumatic compression (IPC), and GCS + IPC + LMWH, were given in the other three groups, LMWH, IPC, and IPC + LMWH (IL) groups, respectively. The thrombosis indices, including blood routine test, coagulation function indicators, and thrombosis indicators, were recorded. Results: The incidence of DVT in the control, LMWH, IPC, and IL groups was 7.1% (26/366), 2.6% (9/352), 2.5% (8/322), 1.5% (5/340), respectively. The incidence of DVT in the experimental groups decreased significantly. The white blood cell (WBC) count increased significantly after surgery compared with that before surgery. The hemoglobin concentration, hematocrit, and mean platelet decreased in all the groups. The prothrombin time and activated partial thromboplastin time prolonged significantly and the fibrinogen level increased; however, the thrombin time dropped. The tissue-type plasminogen activator, plasminogen activator inhibitor, protein C, and protein S all decreased, while the D-dimer increased after surgery. The antithrombin III (AT-III) decreased only in the LMWH and IL groups. Conclusions: A single preventive method was not enough to avoid thrombosis in high-risk patients; however, a superimposition of preventive methods could significantly reduce the incidence of thrombosis.

Keywords: Gynecologic surgery, prophylactic, lower-extremity deep venous thrombosis

Introduction

Venous thromboembolism is presented as deep venous thrombosis (DVT) and pulmonary embolism (PE) [1]. DVT is a venous reflux disorder disease resulting from abnormal blood coagulation in the deep vein, most often occurring in legs, but can also form in the veins of the arms [2]. Taking popliteal vein as the landmark, DVT above the popliteal vein is known as proximal DVT, and DVT after the popliteal vein is known as distal DVT [3]. A lower-extremity deep venous thrombosis (LEDVT) is defined as an intrafascial venous thrombosis of the lower limbs, including deep leg vein, popliteal vein, deep femoral vein, superficial femoral vein, femoral vein, and iliac vein. LEDVT is a common serious complication of gynecologic surgery, and the incidence of thrombosis might drop in PE [4]. Two associated illnesses arise after PE or DVT: chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome [4-10]. Life expectancy is often shortened, and patients frequently die of sudden cardiac death due to these illnesses [11].

When no prophylactic was used, the incidence of DVT among patients undergoing major gynecologic surgical procedures for benign diseases ranged from 6.2% to 29.1%, and the incidence rate increased year by year, showing a positive correlation trend with age [12-14]. The incidence of LEDVT following gynecologic pelvic surgery was reported to be 15.6% in

Chinese patients [5, 15]. Therefore, high attention should be paid to LEDVT occurrence after gynecologic pelvic surgery.

The pathophysiology of venous thrombosis involves three interrelated factors (Virchow's triad) that damage the vessel wall, slowing down the blood flow and increasing the blood coagulability [16, 17]. The most frequently used prophylactic methods used for thrombosis were physical and drug methods [18]. Graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) were the most common physical methods used, whereas low-molecular-weight heparin (LMWH) was the most common drug used to prevent thrombosis [19, 20]. GCS promoted the venous blood flow in the legs by elastic compression, hemodynamic changes, and prevention of coagulation factors to aggregate and adhere to vascular endothelium, thereby effectively reducing the incidence of DVT [21, 22]. IPC intermittently compressed the calf and (or) thigh by rhythmic expansion and contraction using a compressed air pump, with the deep calf vein draining and promoting blood flow in the femoral vein, increasing the fibrinolytic activity, and ultimately reducing the incidence of DVT [23, 24]. LMWH exerted its antithrombotic effects by binding to specific sites on antithrombin III (AT-III) and inducing a conformational change in AT-III, which, in turn, bound to serine proteases factor Xa and thrombin (IIa) to inhibit thrombin and factor X and ultimately reduce the incidence of DVT [25-28]. GCS, IPC, and LMWH were used in this study to prevent thrombosis, and the effect and mechanisms of DVT prophylactics were investigated.

Materials and methods

Study design

This prospective study included patients who accepted gynecologic pelvic surgery in the Department of Obstetrics and Gynecology of Beijing Chao-Yang Hospital from May 1, 2011, to November 30, 2013. The study was approved by the ethics committee of Beijing Chaoyang Hospital, and all participants signed the informed consent voluntarily.

Inclusion and exclusion criteria

Patients at high risk of DVT and those with negative DVT (-) detected by color Doppler before surgery were included. The inclusion criteria considered the DVT risk factors and gynecologic surgery approaches. The DVT risk factors were as follows: (1) accepted a laparotomy or laparoscopic or vaginal surgery, (2) age ≥ 45 years, (3) history of DVT or PE, (4) thrombophilia (such as a history of cerebral infarction or myocardial infarction, platelet count > 400 × 10^9/L), (5) surgery time > 3 h, and (6) history of gynecologic malignancy (no age limit). The surgical approaches were as follows: (7) laparotomy, (8) laparoscopy, (9) vaginal surgery, (10) laparoscopically assisted vaginal surgery, and (11) laparoscopic surgery transformed to laparotomy. Patients meeting criterion 1, any one criterion from criteria 2-6, and any one from criteria 7-11 were included in this study [5]. Patients were excluded from the study if (1) diagnosed with thrombophlebitis, (2) diagnosed with PE before surgery, (3) had experienced acute DVT before surgery, (4) had platelet count < 100 × 10^9/L, (5) had a history of coagulation disorders, (6) were on long-term use of anticoagulant drugs such as aspirin, (7) had a bleeding tendency, (8) had a history of gastrointestinal bleeding, (9) had a history of intracranial hemorrhage, (10) had congestive heart failure, (11) had pulmonary edema or severe leg edema, (12) had severe leg exceptional circumstances (such as dermatitis, gangrene, or skin graft surgery recently), and (13) had severe arteriosclerosis of lower-extremity vascular or other vascular ischemic disease or severe leg deformity. Patients with any one of the aforementioned criteria were excluded.

Grouping

All patients were divided into four groups by envelope method according to their time of admission. Patients who took part in this study picked an envelope involving a note of control, LMWH, IPC or IL when they were admission. Patients who did not meet the conditions were excluded, and 690 patients who met the inclusion criteria were included in this study.

Treatment

GCS were used as basic prophylactics for DVT in the control group. Advanced prophylactics were given in the experimental groups: GCS + LMWH were used as prophylactics in the LMWH group; GCS + IPC were used as prophylactics in the IPC group; and GCS + IPC + LMWH were used as prophylactics in the IPC + LMWH (IL) group.

Table 1. Clinical characteristics of the patients

	Control group (n=183)	LMWH group (n=176)	IPC group (n=161)	IL group (n=170)	*F*	*P*
Age (year)	54.13 ± 9.46	54.70 ± 10.93	52.84 ± 9.85	53.08 ± 10.21	1.26	0.287
BMI (kg/m^2)	24.98 ± 3.56	24.83 ± 3.52	24.81 ± 3.79	25.57 ± 4.71	1.385	0.246
	Control group	LMWH group	IPC group	IL group	χ^2	*P*
Diseases					18.924	0.756
Ovarian cancer	18	11	11	12		
Uterine body cancer	16	19	22	30		
Uterine cervix cancer	19	20	23	26		
Vulvar cancer	2	2	3	2		
Uterine fibroids	52	46	37	38		
Adenomyosis	10	12	10	12		
Ovarian benign tumors	39	34	33	22		
Pelvic prolapse	18	21	13	18		
Others	9	11	9	10		
Surgical methods					16.729	0.16
Laparotomy	67	59	61	42		
Laparoscopy	90	89	83	106		
Vaginal surgery	17	22	11	17		
Laparoscopically assisted vaginal surgery	4	5	5	3		
Laparoscopy transformed to laparotomy	5	1	1	2		
Surgical position					12.114	0.059
Supine position	70	57	64	45		
Trendelenburg	94	90	82	104		
Lithotomy position	19	29	15	21		
Venotransfuse site					4.777	0.189
Left arm	18	13	8	8		
Right arm	165	163	153	162		
Family history					3.541	0.316
No	172	172	153	164		
Yes	11	4	8	6		
Past medical history					1.866	0.601
No	180	171	160	166		
Yes	3	5	1	4		
Smoking					5.585	0.134
No	180	173	161	170		
Yes	3	3	0	0		
Hypertension					2.523	0.571
No	126	126	110	128		
Yes	57	50	51	42		
Diabetes					2.545	0.467
No	151	152	142	143		
Yes	32	24	19	27		
Respiratory diseases					2.457	0.483
No	177	173	156	168		
Yes	6	3	5	2		
Angiocardiopathy					0.338	0.943
No	171	165	150	161		
Yes	12	11	11	9		
Anemia					0.092	0.993
No	164	158	143	152		
Yes	19	18	18	18		
Phlebeurysma					1.269	0.737
No	167	162	151	154		
Yes	16	14	10	16		

BMI, Body mass index; IL, IPC + LMWH; IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin. Values are expressed as mean ± standard deviation. One-way ANOVA and chi-square test were used; $P < 0.05$ was considered as significant differences.

Table 2. Incidence of DVT

	Control group	LMWH group	IPC group	IL group	X^2	*P*
Total legs	366	352	322	340		
DVT in legs	26	9	8	5		
Incidence of DVT (%)	7.1	2.6[a]	2.5[a]	1.5[b]	20.249	< 0.001

DVT, Deep venous thrombosis; IL, IPC + LMWH; IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin. [a]Compared with the control group, $P < 0.05$. [b]Compared with the control group, $P < 0.001$.

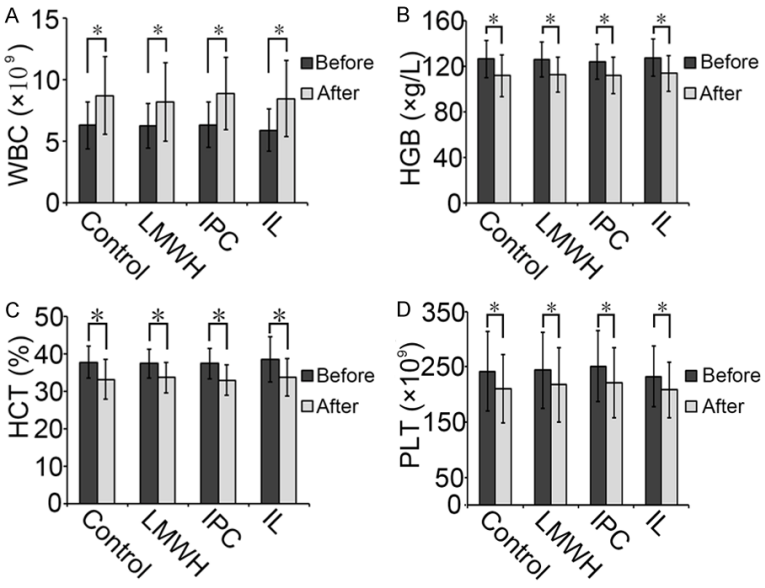

Figure 1. Changes in blood routine test of four groups. (A) White blood cell count changes, (B) hemoglobin change, (C) hematocrit changes, and (D) platelet changes. *, $P < 0.05$.

The preventive methods were as follows:

GCS for preventing DVT: The TED knee-length anti-embolism stockings (Tyco Healthcare Group, MA, USA) were adopted in this method. Appropriate-size anti-embolism stockings were chosen for patients according to the thickest part of the leg circumference: small-size fit for circumference ≤ 30.5 cm, middle-size fit for 30.5 cm < circumference ≤ 38.1 cm, and large-size fit for 38.1 cm < circumference ≤ 44.51 cm. The TED antithrombotic pressure stockings were used from the day of surgery to ambulation for at least 3 days.

IPC for preventing DVT: The Kendall SCD Response pump (Tyco Healthcare Group) was used in this method, which is a sequential stepped pressing device. It automatically adjusts the emptying stress-free time according to the venous filling speed. The device was used from the time of anesthesia administration to ambulation for at least 3 days.

LMWH for preventing DVT: Fragmin (Pharmacia Corp., Germany), the main ingredient is dalteparin sodium, was used in this method, and the dose was 5000 IU/0.2 mL. Patients received injections of 5000 IU Fragmin subcutaneously 12 h after surgery, once daily for 5 days.

Outcome

The primary outcome was the incidence of DVT detected by Doppler ultrasound 7 days after surgery. The incidence of DVT was defined as the rate of DVT occurring in legs detected by color Doppler ultrasound. The color Doppler ultrasound examinations (5.0-10.0 MHz; American ACUSON 12/XP, CA, USA) of lower limbs were performed by sonographers according to Schellong' criterion 7 days before surgery and 3-7 days after surgery [29].

The secondary outcomes were thrombosis indices, including blood routine test, coagulation function indicators, and thrombosis indicators. Venous blood was collected twice 7 days before surgery and 3 days after surgery for blood routine test; coagulation test, including prothrombin time (PT), thrombin time (TT), activated partial thromboplastin time (APTT), and fibrinogen (FBG); and thrombosis test, including tissue-type plasminogen activator (t-PA), plasminogen activator inhibitor (PAI), protein C (Pc), protein S (Ps), AT-III, and D-dimer.

Adverse effect

The symptoms after surgery, such as skin color, physical pain, leg swelling, and vaginal stump bleeding, were closely observed, and proper treatment was given.

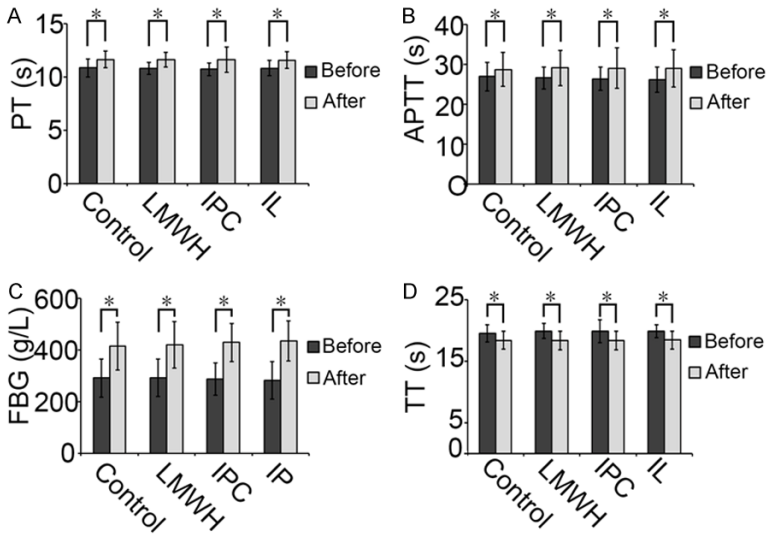

Figure 2. Changes in coagulation function of four groups. (A) Prothrombin time changes, (B) activated partial thromboplastin time changes, (C) fibrinogen changes, and (D) thrombin time changes. *, $P < 0.05$.

Statistical analysis

The data treatment was conducted using statistical software SPSS 19.0 (SPSS Inc, IL, USA). Continuous variables were expressed as mean ± standard deviation, and comparisons were conducted using paired-sample *t* test and one-way analysis of variance (ANOVA) as appropriate. Enumeration data were expressed as percentage, and comparison was conducted using chi-square test. A P value < 0.05 was considered as statistically significant.

Results

Characteristics of patients

The control group included 183 patients, aged 23-81 years (54.13 ± 9.46), with a body mass index (BMI) of 24.98 ± 3.56. The LMWH group included 176 patients, aged 18-86 years (54.70 ± 10.93), with a BMI of 24.83 ± 3.52. The IPC group included 161 patients, aged 26-82 years (52.84 ± 9.85), with a BMI of 24.81 ± 3.79. The IL group included 170 patients, aged 28-81 years (53.08 ± 10.21), with a BMI of 25.57 ± 4.71. Among the four groups, no significant differences were noted for age, BMI, disease types, surgical approach, intraoperative position, venotransfuse site, family history, past medical history, smoking history, and other diseases (one-way ANOVA and chi-square test, $P > 0.05$) (**Table 1**).

Primary outcome

DVT occurred in 26 out of 366 lower extremities in the control group; the incidence was 7.1% (26/366). The incidence of DVT was 2.6% (9/352) in the LMWH group, 2.5% (8/322) in the IPC group, and 1.5% (5/340) in the IL group. The incidence of DVT correlated with different preventive methods. The differences between the control and experimental groups (including LMWH, IPC, and IL groups) were significant. The statistics was significant when more prophylactics were used (chi-square test, $P < 0.05$) (**Table 2**).

Secondary outcome

Changes in blood routine test: No significant difference was observed among the four groups in the blood routine test, including white blood cell (WBC) count, hemoglobin (HGB), hematocrit (HCT), and platelet (PLT), before surgery without any precautions (one-way ANOVA, $P > 0.05$). The WBC count in the four groups after surgery significantly increased compared with that before surgery (paired-sample *t* test, $P < 0.05$), and the HGB, HCT, and PLT after surgery significantly decreased (paired-sample *t* test, $P < 0.05$). No significant difference was observed in the WBC, HGB, HCT, and PLT levels among the four groups after surgery (one-way ANOVA, $P > 0.05$) (**Figure 1**).

Changes in coagulation function: No significant difference was observed in the coagulation function, including PT, TT, APTT, and FBG level, among the four groups before surgery (one-way ANOVA, $P > 0.05$). The PT and APTT of the four groups after surgery significantly prolonged compared with those before surgery (paired-sample *t* test, $P < 0.05$); the FBG levels of the four groups after surgery significantly increased (paired-sample *t* test, $P < 0.05$), and the TT significantly decreased (paired-sample *t* test, $P < 0.05$). However, no significant difference was observed in the APTT, PT, TT, and FBG levels among the four groups after surgery (one-way ANOVA, $P > 0.05$) (**Figure 2**).

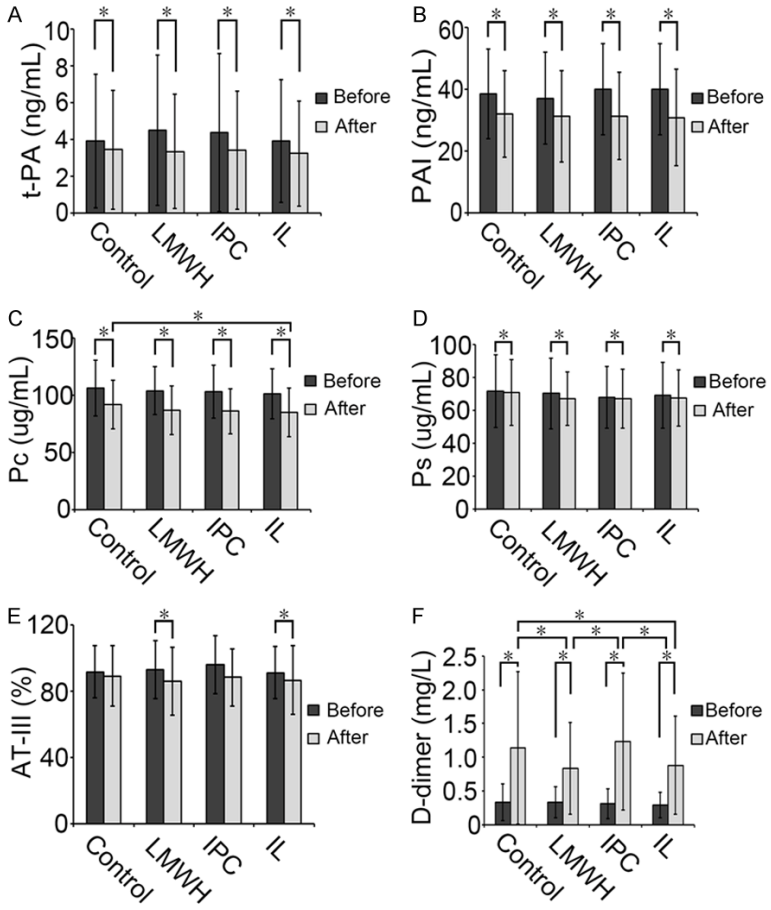

Figure 3. Changes in thrombosis parameters of four groups. (A) Tissue-type plasminogen activator changes, (B) plasminogen activator inhibitor changes, (C) protein C changes, (D) protein S changes, (E) antithrombin III changes, and (F) D-dimer changes of four groups. *, $P < 0.05$.

Table 3. Side effects

Side effects	Control group	LMWH group	IPC group	IL group
Allergic skin itching	1	0	0	0
Vaginal stump bleeding	0	2	0	0
Skin and mucosa bleeding	0	0	0	2

IL, IPC + LMWH; IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin.

Changes in thrombosis parameters: No significant difference was observed in the thrombosis parameters, including t-PA, PAI, Pc, Ps, AT-III and D-dimer, among the four groups before surgery (one-way ANOVA, $P > 0.05$). After surgery, the levels of t-PA and PAI in the four groups significantly decreased (paired-sample *t* test, $P < 0.05$), without any statistical significance (one-way ANOVA, $P > 0.05$) (**Figure 3A** and **3B**). The Pc and Ps levels of the four groups after surgery significantly decreased (paired-sample *t* test, $P < 0.05$), and the difference in the Pc level after surgery between the control and IL groups was significant (one-way ANOVA, $P < 0.05$). However, no significant difference was found among the LMWH, IPC, and IL groups (one-way ANOVA, $P > 0.05$). No significant difference was observed in the Ps level of the four groups after surgery (one-way ANOVA, $P > 0.05$) (**Figure 3C** and **3D**). No significant change was found in the AT-III level before and after surgery in the control and IPC groups (paired-sample *t* test, $P > 0.05$), but the changes in the AT-III level before and after surgery in the LMWH and IL groups were significant (paired-sample *t* test, $P < 0.05$) (**Figure 3E**). The D-dimer levels after surgery in the four groups were significantly higher than those before surgery (paired-sample *t* test, $P < 0.05$), but no significant difference was found in the D-dimer levels after surgery between the control and IPC groups, or between the LMWH and IL groups (one-way ANOVA, $P > 0.05$). However, differences in D-dimer levels after surgery between the control and LMWH groups, and also between the LMWH and IPC groups were significant (one-way ANOVA, $P < 0.05$) (**Figure 3F**).

Side effects

One patient in the control group had allergies with a symptom of itchy skin, two patients in the LMWH group had bleeding in the vaginal stump, no patient in the IPC group had any adverse reaction, and one patient in the IL

group had bleeding from the skin and mucous membrane (**Table 3**).

Discussion

The inflammation caused by the increased WBC after surgery could easily lead to vascular endothelial injury in the present study, which may be the initial reason of thrombosis. Moreover, the decreased levels of HGB, HCT, and PLT were the results of blood loss. The damage in physiological anticoagulant mechanisms might be due to the abnormal Pc, Ps, AT-III, t-PA, and PAI levels, leading to a hypercoagulable state. D-dimer, a specific degradation product of a cross-linked protein, is a sensitive indicator of DVT. The increase in the D-dimer level after surgery indicated the activation of fibrinolytic system [30]. However, the increased FBG level also indicated a hypercoagulable state of blood. Pc and Ps are vitamin K-dependent glycoproteins, which act as natural anticoagulants, and co-inactivate the activation factor V (FVa) and factor VIII (FVIIIa). The decreased t-PA and PAI levels indicated the deficiency of plasma coagulation inhibitors and were probably caused by the activation of the intrinsic coagulation pathway. The Pc and Ps levels are indicators of DVT, and t-PA and PAI levels are indicators of fibrinolytic system activation [31-33]. The decreased t-PA, PAI, Pc and Ps levels and increased D-dimer and FBG levels after surgery more likely resulted in the intravascular thrombus formation, suggesting a hypercoagulable state. This study showed that both the PT and APTT in the four groups prolonged after surgery, suggesting the activation of anticoagulation system, demonstrating that all the prophylactics were effective in preventing thrombosis. The changes in D-dimer and AT-III levels after surgery in the LMWH and IL groups indicated that LMWH could inhibit blood coagulation, improve the coagulation and thrombosis indicators, and then reduce the thrombosis incidence.

This study compared the effects of four preventive methods (control, LMWH, IPC, and IL groups) of thrombosis, and the incidence of thrombosis was 7.1% (26/366), 2.6% (9/352), 2.5% (8/322), and 1.5% (5/340), respectively. The incidence of DVT in the LMWH, IPC, and IL groups was significantly lower compared with that in the control group, indicating that superimposed preventive methods could significantly reduce the incidence of thrombosis, and the IL group had the best effect of preventing thrombosis. The result demonstrated that the incidence of thrombosis was negatively correlated with the increased preventive methods; however, no obvious synergy was found among preventive methods. According to the guidelines of the American College of Chest Physicians (ACCP) for DVT [1], this study considered that high-risk patients with the risk of bleeding should take two physically superimposed preventive methods to prevent DVT; high-risk patients with no bleeding tendency should use a combination of physical methods and drugs; and very high risk patients with no bleeding tendency should take two physically superimposed methods combined with a drug to prevent DVT.

However, the present study had some limitations. First, many operative methods were included in this study, which might have affected the statistical results. Moreover, the follow-up result in this study was only short term, and hence a long-term follow-up is needed to obtain a stable result.

In summary, a single preventive method was not enough to avoid thrombosis in high-risk patients. However, a superimposition of preventive methods could significantly reduce the incidence of thrombosis. More use of prophylactics led to less incidence of DVT.

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Disclosure of conflict of interest

None.

Abbreviations

ACCP, American College of Chest Physicians; APTT, activated partial thromboplastin time; AT-III, antithrombin III; BMI, body mass index; DVT, deep venous thrombosis; FBG, fibrinogen; GCS, graduated compression stockings; HCT, hematocrit; HGB, hemoglobin; IPC, intermittent

pneumatic compression; LEDVT, lower-extremity deep venous thrombosis; LMWH, low-molecular-weight heparin; PAI, plasminogen activator inhibitor; Pc, protein C; PE, pulmonary embolism; PLT, platelet; Ps, protein S; PT, prothrombin time; PTS, postthrombotic syndrome; t-PA, tissue-type plasminogen activator; TT, thrombin time; WBC, white blood cell.

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