

## Original Article

# Elastic stockings plus enoxaparin and intermittent pneumatic compression in preventing postoperative deep venous thrombosis in patients with ovarian cancer

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**Abstract:** Objective: This study aimed to explore the effects of elastic socks plus enoxaparin and intermittent pneumatic compression (IPC) in preventing postoperative lower extremity deep venous thrombosis (LEDVT) in patients with ovarian cancer (OC). Methods: A prospective, single-center, double-blind, case-control study was conducted. Ninety-two patients with OC were enrolled and randomly allocated into a combined group (n=46) or a control group (n=46). The patients in the control group were treated with enoxaparin after surgery, and those in the combined group were treated with elastic stockings, IPC, and enoxaparin. The therapeutic effects between the two groups were compared. The incidence of postoperative DVT, changes in the plasma D-dimer levels at 3 days before and 5 days after surgery, the platelet (PLT) count, prothrombin time (PT), activated partial thromboplastin time (APTT) and mean flow velocity (Vm) were measured at the 5th day after surgery. Swelling and pain of the lower extremities and patient satisfaction were also recorded. Results: The incidences of DVT and the swelling and pain of the lower extremities in the combined group were lower than they were in the control group ( $P<0.05$ ). At 5 days after the surgery, the plasma D-dimer levels in both groups were higher than they were at 3 days before the surgery, and the combined group had a lower level than the control group ( $P<0.05$ ). PLT increased, but the PT, APTT, and Vm decreased in both groups at 5 days after the surgery. The Vm in the combined group was higher than it was in the control group (all  $P<0.05$ ), and there was no statistically significant difference in the PLT, PT or APTT between the two groups ( $P>0.05$ ). The patients in the combined group showed higher satisfaction than those in the control group ( $P<0.05$ ). Conclusion: Elastic stockings plus enoxaparin and IPC effectively prevent postoperative DVT, alleviate lower extremity swelling and pain, and improve the satisfaction of patients with OC, but the combination has no effects on the coagulation mechanism.

**Keywords:** Ovarian cancer, deep vein thrombosis, elastic stockings, enoxaparin, intermittent pneumatic compression

## Introduction

Tumor-associated venous thromboembolism (VTE) is the second leading cause of death in patients with malignant tumors. Deep vein thrombosis (DVT), the major type of VTE, is most common in malignant tumors of the female reproductive system. Ovarian cancer (OC) is a prevalent malignant tumor in the female reproductive system [1]. The deep location and small size of the ovaries in the pelvic cavity lead to the extensive range of cytoreductive surgery. Therefore, DVT is more likely to occur after surgical treatment. The incidence rate of thrombosis is reported to be about 4% [2-4], and it is mainly manifested by lower

extremity swelling and pain and varicose veins, resulting in a partial or complete loss of lower extremity function, possibly complicated by pulmonary embolism, affecting overall survival. Heparin is the preferred treatment for preventing postoperative DVT in patients with OV [5], but there are still some patients who suffer from lower limb swelling, pain, allergy, and bleeding [6]. Therefore, no effective radical treatments are available in clinics.

Medical elastic stockings pressurize the veins of the lower limbs through a pressure gradient generated by elasticity, so as to smooth venous return and promote blood circulation, and the stockings are widely applied at home and

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abroad to prevent postoperative lower extremity DVT (LEDVT) [7]. In China, Cao Yan et al. assessed the efficacy of elastic stockings at preventing LEDVT after abdominal surgery, and found the rate of DVT in the study group was 6.4%, significantly lower than the rate of 20.0% in the control group, suggesting a high efficacy of elastic stockings [8]. Chen Ying et al. found that decompression elastic stockings combined with low molecular weight heparin (LMWH) were valuable in preventing DVT in OC patients, although 4% of the patients still developed DVT 15 days after surgery, which was significantly lower than the 20% in the conventional care group, and there was a probability of DVT [9]. Therefore, the search for more effective preventive measures has become a hot topic. Therefore, 46 patients with OC enrolled in our study were treated with elastic stockings plus enoxaparin and IPC after surgery, so as to provide a reliable reference basis for the clinical prevention of DVT.

### Data and methods

#### General data

A single-center, prospective, randomized controlled, double-blind study was carried out. Ninety-two patients with OC who were admitted to The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology from July 2017 to June 2019 were randomly allocated into a combined group (n=46) or a control group (n=46). All the patients signed an informed consent form. This study was approved by the hospital's Medical Ethics Committee.

#### Case collection

Inclusion criteria: (1) patients diagnosed with OC by two senior pathologists through postoperative pathological sections; (2) patients receiving no adjuvant chemotherapy and radiotherapy; (3) patients with surgery times of 2-5 h; (4) patients with clear minds; (5) patients who voluntarily signed the consent form. Exclusion criteria: (1) patients with mental diseases; (2) patients with language communication impairments; (3) patients with severe cardiovascular or cerebrovascular diseases; (4) patients with poor compliance; (5) patients allergic to LMWH; (6) patients with complications such as coagulation dysfunction or varicose veins; (7) patients with previous hyperlipidemia, hypertension, or diabetes; (8) patients with previous DVT or

other high-risk diseases; (9) patients with other malignant tumors.

#### Methods

The patients in the two groups were given symptomatic treatment such as anti-infection and fluid infusion after surgery, and 2-3 days later, they were instructed to get out of bed. Patients in the control group were treated with a subcutaneous injection of enoxaparin (3000 IU, Changzhou Qianhong Bio-pharma Co., Ltd., SFDA Approval no. H20153098) 24 hours after surgery, once a day. The patients in the combined group were treated with elastic stockings, enoxaparin, and IPC after surgery: the patients put on elastic stockings (Beijing JIANNI Technology Development Co., Ltd) the next morning after surgery. The dosage of enoxaparin was the same as it was in the control group. How to use IPC: elevate the patient's legs on the 2nd day after the surgery, put on the pneumatic compression leg sleeve (WBH-B IPC, Bohua Medical Co., Ltd.), then inject air in sequence, zip the sleeve from the foot back to the uppermost thigh. Afterwards, turn on the IPC, and set the pressure parameters according to the patient's tolerance degree. The treatment intensity was in the range of 10-20 kPa, and the cyclic compression and decompression were carried out according to the sequence of foot-ankle-calf-knee-thigh, with an interval of 3-6 s. The treatment was performed 4 times a day for 30 min each time. Both treatments in the two groups lasted for 1 week.

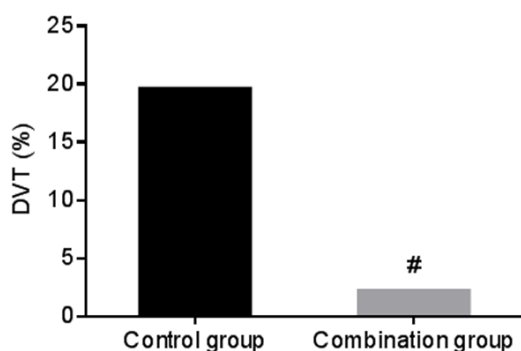
#### Outcome measures

The incidences of DVT and pulmonary embolism (PE) were compared between the two groups. At the same time, fasting elbow venous blood was sampled 3 days before and 5 days after surgery. A Sysmex CA-7000 Blood Coagulometer (Sysmex, JPN) was applied to measure the changes in the plasma D-dimer levels. And an ACL-200 coagulation analyzer (Beckman-Coulter Diagnostics, USA) was employed to analyze the changes in the platelet (PLT) count, prothrombin time (PT), and activated partial thromboplastin time (APTT) 5 days after surgery. A color Doppler ultrasound (Philips ATL 5000) measured the mean flow velocity ( $V_m$ ) of the lower limbs, and the lower limb swelling and pain and patient satisfaction were compared between the two groups. The therapeutic effect was assessed according to the symptoms of postoperative lower limb pain and swelling, varicose veins, as well as the presence of intralu-

**Table 1.** Comparison of clinical data in the two groups

Group	Control group	Observation group	t/ $\chi^2$	P
Average age (years)	46.52±5.12	46.62±5.55	0.090	0.929
Average weight (kg)	64.23±5.17	64.35±5.24	0.111	0.912
AJCC Cancer Staging			0.499	0.618
I Stage	4	3		
II Stage	3	5		
III Stage	31	32		
IV Stage	8	6		
Surgery time (h)	3.14±0.83	3.12±0.95	0.108	0.915
Surgery type			0.734	0.865
Accessory resection	23	22		
Tumor cytoreductive surgery	13	15		
Staged exploration	10	9		
History of intravenous heparin use (cases)	6	9	0.717	0.397

Note: AJCC: American Joint Committee on Cancer.



**Figure 1.** Comparison of the postoperative DVT in the two groups. Compared with the control group, #P<0.05; DVT: deep venous thrombosis.

minal echoes. The treatment was considered effective in the absence of the above symptoms, otherwise it was considered ineffective. Patient satisfaction was evaluated using a self-designed satisfaction questionnaire from our hospital. A total of 96 questionnaires were delivered and 96 were returned, for a recovery rate of 100.00%. With 100 points in total, above 90 points indicated satisfaction, 60-89 points indicated general satisfaction, and below 60 points indicated dissatisfaction. Finally, patient satisfaction = satisfaction rate + general satisfaction rate. All the patients were divided into a thrombus group and a non-thrombus group for the multivariate analyses.

#### Statistical analysis

SPSS 19.0 was used to process the data. The measurement variables were expressed as the means ± standard deviations ( $\bar{x} \pm sd$ ). Paired t

tests were used for the intra-group comparisons, and independent t tests for the inter-group comparisons. The counting data expressed as number/percentage (n/%) were tested using  $\chi^2$ . Taking the body mass index (BMI), age, fibrinogen, thrombus history, smoking history, blood transfusion volume, bedrest time, and the use of elastic stockings as dependent variables and the DVT incidence rate as an independent variable, a multivariate logistic regression analysis was carried out. P<0.05 indicated that the difference was statistically significant.

## Results

### Clinical data

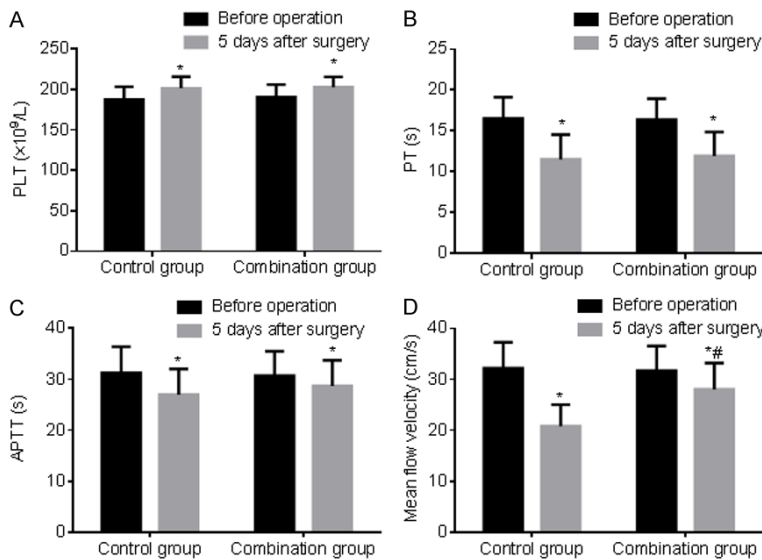
There were no significant differences in terms of age, weight, American Association of Cancer (AJCC) Cancer Staging, histological type, surgery time, surgery type, or history of intravenous heparin use between the two groups (P>0.05), indicating their comparability. See **Table 1**.

### Incidence of postoperative DVT

The incidence of postoperative DVT in the combined group was 2.2% (1/46), lower than the 19.6% (9/46) in the control group (P<0.05). It suggested that the elastic stockings plus enoxaparin and IPC significantly reduced the incidence of postoperative DVT in the OC patients, and the curative effect was superior to that of enoxaparin monotherapy. See **Figure 1**.

**Table 2.** Comparison of the changes in the plasma D-dimer levels between the two groups ( $\bar{x} \pm s$ , mg/L)

Group	3 days before surgery	5 days after surgery	t	P
Control group (n=46)	0.25±0.07	0.50±0.10	13.891	0.000
Combined group (n=46)	0.24±0.05	0.40±0.08	11.503	0.000
t	0.788	5.296		
P	0.433	0.000		



**Figure 2.** Changes of PLT, PT, APTT and Vm. A. PLT: platelet; B. PT: prothrombin time; C. APTT: activated partial thromboplastin time; D. Vm: mean flow velocity. Compared with before the operation, \*P<0.05; compared with the control group, #P<0.05.

**Table 3.** Comparison of the patients' lower extremity swelling and pain in the two groups (n, %)

Group	Swelling	Pain
Control group (n=46)	10 (21.74)	11 (23.91)
Combined group (n=46)	3 (6.52)	2 (4.35)
t	4.390	7.256
P	0.000	0.000

*Changes of plasma D-dimer*

The plasma D-dimer levels at 5 days after surgery were higher than that at 3 days before surgery in both groups, but the level in the combined group was lower than it was in the control group (P<0.05). This suggests that the elastic stockings plus enoxaparin and IPC remarkably improved the OC patients' plasma D-dimer levels after surgery, effectively decreased the risk

of thrombosis, and the curative effect was superior to that of enoxaparin monotherapy. See **Table 2.**

*Changes in PLT, PT, APTT and Vm*

PLT increased and PT, APTT, and Vm decreased significantly in both groups at 5 days after the operations (P<0.05). There was no significant difference in PLT, PT, or APTT between the two groups (P>0.05), but the Vm in the combined group was higher than it was in the control group (P<0.05). These results suggest that elastic stockings plus enoxaparin and IPC significantly enhanced the blood circulation in the lower limbs of the OC patients after surgery, and the curative effect was superior to that of enoxaparin monotherapy. See **Figure 2.**

*Incidence of lower extremity swelling and pain*

The incidence of lower extremity swelling and pain in the combined group was lower than it was in the control group (P<0.05), indicating that elastic stockings plus enoxaparin and IPC dramatically relieved the OC patients' postoperative lower extremity swelling and pain, and the curative effect was superior to that of enoxaparin monotherapy. See **Table 3.**

*Patient satisfaction*

The satisfaction rate in the combined group was 95.65% (44/46), higher than the 78.26% (36/46) in the control group (P<0.05), indicating that elastic stockings plus enoxaparin and IPC significantly increased the patients' satisfaction and the nurse-patient coordination. See **Table 4.**

*Multivariate analysis of occurrence of DVT*

A multivariate logistic regression analysis demonstrated that BMI, serum fibrinogen, bedrest time and the use of elastic stockings were inde-

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**Table 4.** Comparison of the patient satisfaction in the two groups (n, %)

Group	Satisfaction	Generally satisfied	Dissatisfied	Overall satisfaction rate
Control group (n=46)	17 (36.96)	19 (41.30)	10 (21.74)	36 (78.26)
Combined group (n=46)	30 (65.22)	14 (30.43)	2 (4.35)	44 (95.65)
$\chi^2$				6.133
P				0.000

**Table 5.** Multivariate analysis of the occurrence of DVT

Influencing factors	P	Risk ratio	95% confidence interval
BMI	0.017	1.922	1.279-2.417
Age	0.382	1.141	0.766-1.513
Fibrinogen	0.022	2.446	1.688-3.499
History of thrombosis	0.915	1.093	0.073-11.246
Smoking history	0.673	1.655	0.054-9.133
Transfusion volume	0.326	1.242	0.882-1.143
Bedrest time	0.013	2.693	2.243-4.023
The use of elastic stockings	0.014	2.708	2.155-3.977

Note: BMI: body mass index; DVT: deep venous thrombosis.

pendent factors influencing the occurrence of postoperative DVT ( $P < 0.05$ ). It suggested that monitoring BMI, serum fibrinogen, bedrest time and the use of elastic stockings could effectively reduce the risk of developing DVT. See **Table 5**.

### Discussion

The perioperative coagulation in patients undergoing radical OC surgery is at a high level [10, 11]; additionally, the long surgery duration and immobilization are more likely to lead to DVT [12, 13]. Moreover, the long-term bedrest and the application of an analgesic pump to slow down the blood reflux of the patients' lower limbs results in blood stasis after the operation [14, 15], thus increasing the risk of DVT. The aim of this study was to investigate the efficacy of elastic stockings combined with enoxaparin and IPC in preventing postoperative DVT in patients with OC.

Elastic stockings have advantages that bandages do not have. By providing maximum support to the ankle, and then gradually reducing the pressure from the ankle to the calf and then to the thigh, the pressure values of the calf and thigh are 70%-80% and 25%-40% of the ankle, respectively. The pressure changes effectively accelerate the speed of venous blood flow in the lower limbs, thus reducing the

incidence of DVT [16, 17]. Other preventive measures include: (1) Alleviating blood hypercoagulability during the perioperative period; (2) Avoiding blood stasis; (3) Minimizing the damage to blood vessels caused by the surgical operation [18]. Clinical methods such as raising lower limbs, winding bandages, and oral anticoagulants have been often used to prevent DVT, but the curative effect

remains disappointing. Moreover, improper bandage winding may aggravate the severity of DVT [19]. According to the American College of Chest Physicians, mechanical anticoagulation is available for patients with malignant tumors who undergo gynecologic surgery, which mainly includes elastic stockings and IPC [20]. Enoxaparin, a kind of LMWH, is able to significantly enhance the affinity between antithrombin III, coagulation factor Xa, and thrombin, promoting the rapid inactivation of thrombin and further playing the role of preventing DVT [21, 22]. The IPC squeezes the deep vessels, muscles, and lymphatic vessels of the lower limbs through airbags, thus effectively accelerating blood reflux. Rapid decompression contributes to rapid venous vascular filling, i.e. compression and decompression increase the blood flow velocity of the lower limbs and avoid blood stasis, resulting in decreased DVT [23].

The results of this study showed that the treatment efficiency and patient satisfaction in the combined group were higher than they were in the control group; the incidences of postoperative DVT, PE, and lower extremity swelling and pain in the combined group was lower than it was in the control group. The findings indicate that elastic stockings combined with enoxaparin and IPC effectively prevent postoperative DVT, reduce the incidence of PE and lower



extremity swelling and pain, and improve OC patient satisfaction. Chen Ying et al. found that decompression elastic stockings combined with LMWH have a significant effect on preventing postoperative DVT formation, with an incidence rate of about 4% [9], which is similar to the results of our study. The plasma D-dimer level at 5 days after surgery was higher than it was at 3 days before surgery in both groups, but the level in the combined group was lower than it was in the control group. PLT increased and PT, APTT, and Vm decreased significantly in both groups at 5 days after surgery. There was no significant difference in PLT, PT, or APTT between the two groups. Taking this into consideration, elastic stockings plus enoxaparin and IPC effectively prevent DVT after OC surgery by reducing the thrombus markers and blood flow velocity and have no association with the coagulation mechanism.

In this study, the multivariate analysis showed that BMI, serum fibrinogen, bedrest time, and the use of elastic socks in the two groups had statistically significant differences and were independent factors influencing postoperative DVT. Therefore, during the perioperative period, the corresponding high-risk factors need to be screened through a preoperative evaluation of the patient's weight, age, history of venous thrombosis, and smoking history, in order to take the preventive measures accordingly. Moreover, elastic stockings should be worn soon after surgery to reduce the incidence of LEDVT. Jiang Qiulan et al. found that BMI, intraoperative blood loss, average hospital stay, postoperative fibrinogen, and APTT were all influencing factors for DVT after cytoreductive surgery in patients with advanced OC, factors that are helpful in evaluating the formation of postoperative DVT [24]. Xi Yanni et al. also found that BMI, the PLT count, fibrinogen, and bedrest time were independently associated with LEDVT after OC surgery [25].

However, there are still several limitations in this study. For example, the number of cases included was small, and the observation time was short, so the impact of different surgical types on DVT was not analyzed, nor was the long-term efficacy of this therapy. Therefore, the number of cases will be expanded and the observation time will be prolonged in future research.

To sum up, elastic stockings plus enoxaparin and IPC effectively prevent postoperative DVT, alleviate lower extremity swelling and pain, and improve OC patient satisfaction, but the treatment has no effects on the coagulation mechanism.

### Disclosure of conflict of interest

None.

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