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Full Length Article

Comprehensive functional exercises with patient education for the prevention of venous thrombosis after major gynecologic surgery: A randomized controlled study

Miao Guo[1], Ling Lu[1], Yu Sun, Lei Li*, Ming Wu, Jinghe Lang

Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Science, Beijing 100730, China

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ABSTRACT

Objective: To explore the functional exercises of deep breathing and lower limb motions for the prevention of venous thrombosis in patients undergoing major surgery for gynecologic malignancy.

Methods: All eligible patients admitted to the gynecologic oncology unit were randomized into the study and control groups. A comprehensive set of functional exercises was provided to the study group under the instruction and supervision of medical staff. All patients received pre- and postoperative educational material, followed by questionnaires about the patient's perception and satisfaction of the material, and all indicated prophylactic medications were administered.

Results: In total, 132 patients were randomized, and 62 and 53 patients in the study and control groups, respectively, were included in the final analysis. Venous thrombosis, identified by symptoms and/or postoperative ultrasound, was found in 9 (17.0%) and 2 (3.2%) patients in the control and study groups, respectively, which was significantly different ($p = 0.012$), and most of these instances (9/11, 81.8%) were intramuscular vein thrombosis. The incidence of venous thromboembolism (VTE) was not significantly different (1 [1.9%] versus 1 [1.6%]) between the two groups. In the regression model, functional exercise was the only factor associated with venous thrombosis (odds ratio 0.170, 95% confidence interval 0.035–0.815, $p = 0.032$) adjusted with diagnosis and surgical parameters. The detailed educational material had improved the perception and satisfaction of patients about the prevention of VTE.

Conclusion: In a phase 3, single-center randomized controlled study, a comprehensive set of functional exercises combining deep breathing and lower limb motions would significantly decrease the risk of venous thrombosis in patients undergoing major surgery for gynecologic malignancy, especially the risk of intravascular thrombosis.

1. Introduction

A systematic review found that in the Asian population, venous thromboembolism (VTE) rates ranged from 11 to 88 cases per 10,000 admissions. Population-based estimates of postsurgical deep venous thrombosis (DVT) rates ranged from 0.15 to 1.35% [1]. Major gynecologic surgery for malignancy has a high risk of VTE, especially when the surgical duration was longer than 45 min [2]. VTE occurred in 1 in 7 women with epithelial ovarian cancer within 6 months of primary debulking surgery [3]. The incidence of VTE after surgeries for gynecologic cancer was 4% within 90 days after the surgery, and 76% occurred within postsurgery day 7 [4]. DVT or pulmonary embolism (PE) represents a surrogate marker of aggressive tumor behavior and a diminished patient condition in many types of gynecologic malignancies [5,6].

Numerous studies and guidelines have illustrated effective prevention methods for VTE after gynecologic surgeries. Immobility is a great risk factor for VTE in hospitalized patients. However, immobility is not consistently defined in clinical studies, and there have been very few reports on functional exercises, including passive and active lower limb motion and potential breathing exercises, in patients after major gynecologic surgeries. Enhanced popliteal blood velocity and volume flow are key factors in the prevention of venous stasis and DVT [7]. The passive foot flexion applied to persons adapted to endurance physical

* Corresponding author at: Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Science, Shuaifuyuan No. 1, Dongcheng District, Beijing 100730, China.
E-mail addresses: lileigh@163.com (L. Li), wuming@pumch.cn (M. Wu).
[1] M Guo and L Lu contributed equally to this study.

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loads increases venous reserve volume and maximal venous emptying rate [8]. Forceful ankle dorsiflexion, plantarflexion with 250 Newtons and forceful flexion of all toes yielded the highest mean peak systolic velocity values [9]. However, the role of such exercise in the prevention of DVT has not been confirmed in prospective studies. In a small cohort study, forced deep breathing significantly increased peak blood velocity in the superficial femoral vein in patients with plaster cast immobilization of the lower limb in both supine and sitting positions [10]. However, the clinical significance is unknown.

Education is one of the important protocol elements of the Agency for Healthcare Research and Quality Safety Program for Improving Surgical Care and Recovery in gynecologic surgery [11]. Provider education is likely a required additional component and should be combined with other intervention types. Active mandatory tools are likely more effective than passive ones [12]. According to the guidelines of the American Society of Clinical Oncology, oncology professionals should provide patient education about the signs and symptoms of VTE [13]. However, very few studies in the field of gynecologic surgery have included education.

In this study, we reported the results of a randomized controlled trial in a single center, in which a comprehensive set of functional exercises was implemented in the study group, while patient education was provided to all patients.

2. Methods

2.1. Study design

This was a phase 3 randomized controlled study performed at a single teaching hospital. The Institutional Review Board of Peking Union Medical College Hospital approved this study (No. JS-1690). The registration number is NCT03740633 (*clinicaltrials.gov*). All participants had provided their consent before any intervention.

All patients admitted for major surgery for gynecologic malignancy were included in the study. The patients were randomized at a ratio of 1:1 into the study group and control group. A comprehensive set of functional exercises that included deep breathing and active and passive lower limb motion was performed in the study group under the supervision of medical staff. Patient education about the prevention of VTE, postoperative instructions for early activity, and prophylactic medical therapy were provided for all patients equally. To test the quality of the patient education, a structured questionnaire (Supplement Table 1) was completed after patient education, both before surgery and before discharge. The satisfaction of the patients with the patient education was evaluated on the day of discharge.

The epidemiologic and clinicopathological data were collected from case report forms. Twenty-four hours before the surgery and 7 days after the surgery, an ultrasound and a D-dimer test were administered to all patients for the detection of possible VTE in the lower limbs and iliac vessels during the hospital stay or in the outpatient clinics. For patients with suspected VTE, an ultrasound or computed tomographic pulmonary angiography (CTPA) would be administered regardless of the timing. On day 1 before the surgery and on days 1, 3 and 5 after the surgery, the leg circumference 5 cm above the upper margin of the patella and the maximum circumference of the calf was measured by dedicated staff. The Autar scale [14] was evaluated on the day of admission and on day 1 after the surgery.

The primary objective was to determine the incidence of venous thrombosis (including VTE and intramuscular thrombosis) within 7 days after the surgery, which would be detected by symptoms and universal ultrasound. All suspected thrombosis was confirmed or ruled out by ultrasound. The secondary objective was to identify risk factors for VTE. Specifically, a deep muscular venous thrombosis belonged to DVT, which occurred in the major braches of lower limb deep veins, while other intramuscular thrombosis were included in separate analysis.

2.2. Study population and sample size

The patients admitted in the oncology unit of the Department of Obstetrics and Gynecology for the major surgery were included in the study. A careful physical examinations of lower limbs was performed in all patients by a physician and a senior nurse for possible skin lesions or varicose veins. The inclusion criteria consisted of the following: the Eastern Cooperative Oncology Group (ECOG) performance status [15] of 0 or 1; no radiotherapy or chemotherapy before the surgery; no evidence of VTE on the ultrasound before surgery; less than a 24-hour stay in the intensive care unit (ICU); no history of VTE; aged 18 or older; no musculoskeletal injuries or any skin lesions of the lower limbs; and consent for participation was provided. The exclusion criteria consisted of not meeting the inclusion criteria and limitations to activity as judged by the surgeons.

Based on the data from Peedicayil et al. [4], we presumed that there would be venous thrombosis in 20% and 10% of the participants in the control and study groups, respectively, and therefore, each group needed at least 199 participants to achieve a class I error probability (α value) of 0.05 with a statistical power of 0.8.

2.3. Interventions and adverse events

2.3.1. Patient education

After admission, the patient and her relatives watched a video on the prevention, symptoms, consequences and treatment of VTE. After the lecture, a structured questionnaire about the patient's perception of DVT and PE (Supplement Table 1) was completed by the patient, and the results were scored. On day 2 after the surgery, a lecture containing the same content as the video was provided to the patient and her relatives, and a short discussion was acceptable. The same questionnaire in Supplement Table 1 was completed and scored again. The video and lecture were available to all the patients in the study and control groups. Before discharge, a short questionnaire about their satisfaction with patient education was sent to the patients to complete.

2.3.2. Prophylactic therapy and activity

All patients were asked to wear graduated compression stockings before the surgery. Based on the surgeon's instructions, prophylactic low molecular weight heparin (LMWH) was given to patients irrespective of the randomized groups. Intermittent pneumatic compression was not utilized in our study. For all patients, they were asked to be capable of turning over on the bed on the day of surgery, getting out of bed on day 1 after the surgery, and beginning indoor activity from day 2 after the surgery.

2.3.3. Functional exercises

Before the beginning of the study, nurses in charge of the supervision received intensive training on the implementation of the functional exercises. Patients in the study group received the functional exercises under the instruction and supervision from medical staff in a one-to-one manner. These exercises consisted of active ankle motions, passive calf massage and deep breathing. All these exercises were implemented three times per day until discharge. Patients in the control group could also practice the functional exercises, but there were no individual instruction or supervision.

- Active ankle motions included flexion and extension to the maximal limits (holding for at least 5 s) for at least 5 min and circumduction at a speed of 30 times/min for at least 5 min.
- Calf massage was performed by the patient's relatives and/or nursing staff from the distal to proximal ends for at least 5 min.
- Deep breathing consisted of an inspiration of 3–5 s, pause of 1–2 s, and expiration of 3–5 s. Deep breathing exercises lasted at least 5 min.

2.3.4. Adverse events

Adverse events associated with the functional exercises consisted of musculoskeletal and skin injuries, falls, massive bleeding, and pain. A Data Safety Monitoring Committee was in charge of adverse events and venous thrombosis events.

2.4. Statistical analysis

Comparisons of continuous variables were conducted with parametric methods if assumptions of normal distribution were confirmed. Nonnormally distributed variables and categorical data were compared between the study and control groups with the use of nonparametric tests. A binary regression model was used to determine the risk factors of venous thrombosis. Unless otherwise stated, all analyses were performed with a two-sided significance level of 0.05 and conducted with SPSS 23.0 software (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

From November 20, 2018, to January 15, 2019, 156 patients underwent major surgery for gynecologic malignancies, of which 132 patients agreed to participate in the trial and were randomized. Finally, data from 115 patients were used for the analysis (Fig. 1), with 62 and 53 patients in the study and control groups, respectively. The baseline characteristics of the patients are summarized in Table 1, and the examinations for venous thrombosis and the results are listed in Table 2. More detailed data are listed in Supplement Table 2. As shown in Tables 1 and 2, almost all parameters were well balanced, including the epidemiological, clinicopathologic, D-dimer pre- and postoperative results, Autar scale results and risk stratification, circumferences of the lower limbs, LMWH usage and types. In the control and study groups, 43 and 49 patients had received ultrasound examinations after the surgery. There were 4 and 5 patients in the control and study groups respectively who hadn't accepted or just stopped prophylactic LMWH due to the estimation for the risk of bleeding judged by the physicians.

3.2. Venous thrombosis events

Most of the patients (59/62, 95.2%) could complete at least two rounds of exercise per day as recommended in the training protocol. Venous thrombosis, identified by symptoms and/or postoperative ultrasound, were observed in 9 (17.0%) and 2 (3.2%) patients in the control and study groups, respectively, and this difference was significant ($p = 0.012$, Table 2). The median durations from the surgeries to the accidents of venous thrombosis in the control and study groups were 4 days (2 to 8) and 4.5 days (2 and 7). In the control group, the nine cases of venous thrombosis consisted of 1 case of DVT in the right common iliac vein (abdominal debulking for ovarian cancer) and 8 cases of intramuscular vein thrombosis of the calves (4, 3 and 1 cases of ovarian, endometrial and cervical cancer). The DVT case and four cases of intramuscular vein thrombosis were identified by the symptoms of leg swelling and/or pain, and all cases were confirmed by ultrasound. In the study group, the two cases of venous thrombosis consisted of one case of DVT in the right popliteal and posterior tibial vein (laparoscopic staging for ovarian cancer) and one case of intramuscular vein thrombosis of the calves (ovarian cancer). The incidence of intramuscular vein thrombosis was significantly different ($p = 0.008$, Table 2), but the incidence of VTE was not significantly different (1/53 [1.9%] versus 1/

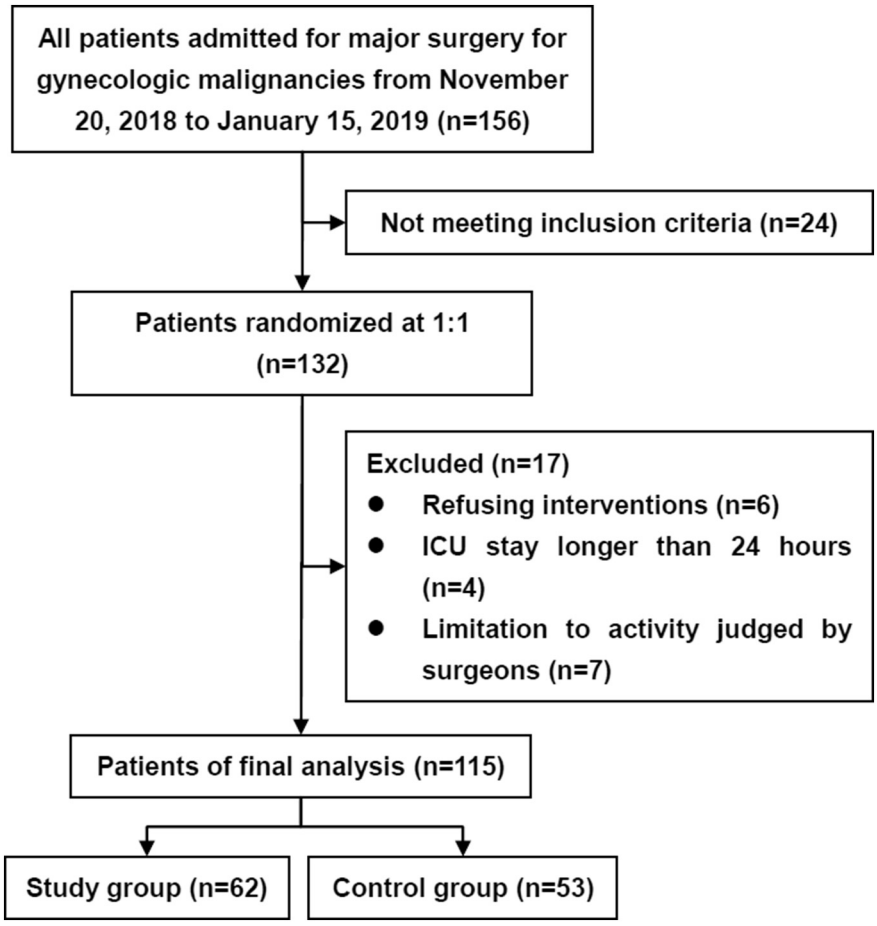

Fig. 1. Flow diagram of the study. ICU, intensive care unit.

Table 1
Epidemiological and clinicopathologic characteristics of the patients. DVC, deep venous catheter. EBL, estimated blood loss. LMWH, low molecular weight heparin. PALN, para-aortic lymph node. PDS, primary debulking surgery. SD, standard deviation.

	Control group (n = 53)	Study group (n = 62)	p
Age (years) mean ± SD	51.6 ± 13.3	47.6 ± 10.9	0.183
Body height (m) mean ± SD	1.60 ± 0.05	1.61 ± 0.05	0.966
Body weight (kg) mean ± SD	59.4 ± 10.9	60.5 ± 8.9	0.206
Body mass index (kg/m^2) mean ± SD	23.2 ± 3.9	23.1 ± 3.2	0.112
ECOG performance status n (%)			1.000
0	49 (92.5%)	57 (91.9%)	
1	4 (7.5%)	5 (8.1%)	
Education n (%)			0.943
High school or lower	26 (49.1%)	30 (48.8%)	
College or higher	27 (50.9%)	32 (51.6%)	
Varicose veins n (%)	3 (5.7%)	4 (6.5%)	0.587
Cardiovascular complications n (%)	11 (20.8%)	7 (11.3%)	0.164
History of aspirin usage n (%)	5 (9.4%)	6 (9.7%)	0.965
Diagnosis n (%)			0.129
Ovarian cancer	30 (56.6%)	27 (43.5%)	
FIGO stage 1 or 2	6/30 (20.0%)	8/27 (29.6%)	
FIGO stage 3 or 4	24% (80.0%)	19/27 (70.4%)	
Endometrial cancer	11 (20.8%)	11 (17.7%)	
FIGO stage 1 or 2	11/11 (100.0%)	10/11 (90.9%)	
FIGO stage 3 or 4	0/11 (0.0%)	1/11 (9.1%)	
Cervical cancer	12 (22.6%)	24 (38.7%)	
IA2	2/12 (16.7%)	3/24 (12.5%)	
IB1	9/12 (75.0%)	18/24 (75.0%)	
IB2	1/12 (8.3%)	3/24 (12.5%)	
Surgical routs n (%)			0.163
Open surgery	30 (56.6%)	27 (43.5%)	
Laparoscopy	23 (43.4%)	35 (56.5%)	
Surgery protocols n (%)			0.064
PDS or staging	41 (77.4%)	38 (61.3%)	
Radical hysterectomy	12 (22.6%)	24 (38.7%)	
Surgical duration (min) mean ± SD	419 ± 700	338 ± 806	0.521
EBL (ml) mean ± SD	1556 ± 754	1286 ± 1442	0.547
Transfusion n (%)	9 (17.0%)	7 (11.3%)	0.379
Transfusion volume (ml) mean ± SD	1556 ± 754 (n = 9)	244 ± 83 (n = 7)	0.547
PALN resection n (%)	48 (97.6%)	52 (83.9%)	0.288
Placement of DVC n (%)	19 (35.8%)	16 (25.8%)	0.243
LMWH usage n (%)	49 (92.5%)	57 (91.9%)	1.000
LMWH types n (%)			0.073
Fraxiparine	21/49 (42.9%)	15/57 (26.3%)	
Lovenox	28/49 (57.1%)	42/57 (73.7%)	
Post-operative stay (day) mean ± SD	6.2 ± 2.5	5.8 ± 2.5	0.420

Table 2
Examinations for venous thrombosis and the results. BUS, B-type ultrasound.

	Control group (n = 53)	Study group (n = 62)	p
D-dimer before surgery (mg/L) mean ± SD	0.8 ± 1.6 (n = 51)	1.0 ± 1.9 (n = 59)	0.349
D-dimer after surgery (mg/L) mean ± SD	2.2 ± 1.4 (n = 43)	2.1 ± 1.8 (n = 53)	0.325
Autar scores before surgery mean ± SD	10 ± 2	9 ± 2	0.502
Risk stratification before surgery n (%)			0.194
Low risk	29 (54.7%)	42 (67.7%)	
Medium risk	24 (45.3%)	19 (30.6%)	
High risk	0 (0%)	1 (1.6%)	
Autar scores after surgery mean ± SD	16 ± 2	16 ± 2	0.315
Risk stratification after surgery n (%)			0.524
Low risk	0 (0%)	0 (0%)	
Medium risk	11 (20.8%)	16 (25.8%)	
High risk	42 (79.2%)	46 (74.2%)	
Left leg circumference (cm) mean ± SD			
Day 0	45 ± 5 (n = 50)	45 ± 4 (n = 62)	0.488
Day 1	45 ± 5 (n = 44)	44 ± 4 (n = 48)	0.079
Day 3	45 ± 5 (n = 49)	44 ± 3 (n = 49)	0.020
Day 5	44 ± 5 (n = 49)	44 ± 3 (n = 42)	0.308
Right leg circumference (cm) mean ± SD			
Day 0	44 ± 4 (n = 50)	45 ± 4 (n = 62)	0.912
Day 1	45 ± 5 (n = 44)	45 ± 4 (n = 48)	0.041
Day 3	44 ± 5 (n = 49)	44 ± 4 (n = 49)	0.082
Day 5	44 ± 5 (n = 49)	44 ± 4 (n = 42)	0.128
Left calf circumference (cm) mean ± SD			
Day 0	35 ± 4 (n = 50)	35 ± 2 (n = 62)	0.009
Day 1	35 ± 4 (n = 44)	34 ± 2 (n = 48)	0.020
Day 3	34 ± 3 (n = 49)	34 ± 2 (n = 49)	0.130
Day 5	34 ± 3 (n = 49)	33 ± 3 (n = 42)	0.074
Right calf circumference (cm) mean ± SD			
Day 0	34 ± 4 (n = 50)	35 ± 3 (n = 62)	0.038
Day 1	35 ± 4 (n = 44)	34 ± 2 (n = 48)	0.024
Day 3	34 ± 3 (n = 49)	34 ± 2 (n = 49)	0.110
Day 5	34 ± 3 (n = 49)	33 ± 3 (n = 42)	0.188
Venous thrombosis in all n (%)	9 (17.0%)	2 (3.2%)	0.012
Intramuscular thrombosis in all n (%)	8 (15.1%)	1 (1.6%)	0.008
Venous thrombosis in BUS n (%)	9/43 (20.9%)	2/49 (4.1%)	0.013
Intramuscular thrombosis in BUS n (%)	8/43 (18.6%)	1/49 (9.8%)	0.009

62 [1.6%]; p = 0.712, Fisher's exact test), in the control and study groups. Although not every patient received postoperative ultrasound examinations, there were still significant differences in the ultrasound discoveries among the total venous thrombosis events and intramuscular vein thrombosis events (p values of 0.013 and 0.009, respectively). No PE occurred based on the symptoms. There were 4 patients that received CTPA due to various symptoms, but no PE were found. The mean values of pre-operative D-dimer were similar in patients with and without DVT or any venous thrombosis, but the patients with DVT or any venous thrombosis had significant higher post-operative D-dimer values (3.6 ± 1.4 versus 1.9 ± 1.5 [p < 0.001] and 3.5 ± 1.5 versus 2.0 ± 1.5 [p = 0.05]). Due to limited sample of venous thrombosis, we couldn't find an appreciate cut-off of D-dimer for the prediction of events.

Regarding the intervention-associated adverse events, there were 3 and 2 cases of massive bleeding > 500 ml after surgery in the control and study groups, respectively (p = 0.426); the massive bleeding was estimated by the increased drainage and decreased hemoglobin levels. After stopping the LMWH, all patients eventually recovered. No musculoskeletal or skin injuries, falls or exercise-associated pain occurred.

Because of the significant effects of the functional exercises, we discontinued patient enrollment ahead of schedule based on the suggestion of the Data Safety Monitoring Committee. Although we did not enroll the number of patients described in the protocol, our results had achieved enough statistical power, 0.8053, with a bilateral α value of 0.05.

3.3. Risk factors for venous thrombosis

As shown in Tables 1 and 2, there were no risk factors for venous thrombosis except for randomization. After adjusting for ECOG status, diagnosis of cancer, surgical route and protocols, postoperative Autar risk stratification and LMWH usage, functional exercise was the only factor associated venous thrombosis in the patients undergoing major surgery for gynecologic malignancy (odds ratio 0.170, 95% confidence interval 0.035–0.815, p = 0.032).

3.4. Questionnaire evaluation

Before and after the surgeries, 107 and 92 patients, respectively, completed the questionnaire about the patient VTE education. Self-controlled comparisons found that the postoperative scores were significantly higher than the preoperative scores: 88.4 ± 6.9 versus 85.2 ± 8.5, respectively; $p < 0.001$. All 115 patients were satisfied or extremely satisfied about the content, manners, and actual results of the patient education. No one chose the options of “not care”, “unsatisfied” or “extremely unsatisfied”.

4. Discussion

In this randomized controlled study, we reported that a set of functional exercises consisting of deep breathing and low limb motions could significantly decrease the incidence of venous thrombosis in patients undergoing major surgery for malignancies. There have been few reports on the relationship between breathing exercises and VTE [11]. Patients admitted for acute exacerbations of chronic obstructive pulmonary disease appear to be at an increased risk for the development of VTE [16]. These findings suggested the potential effectiveness of regular deep breathing in postoperative patients with pelvic surgeries for the prevention of venous thrombosis. Lower limb motions for the prevention of VTE have been reported in several studies. A simple strategy of toe and ankle exercises was introduced to maintain venous return despite below-knee cast immobilization [17]. In a small retrospective study, manual calf massage and passive ankle motion could decrease the prevalence of DVT from 6.52% to 0.79% [18]. The common peroneal or fibular nerve stimulator that activates the calf muscle pump had been successfully used for reducing venous thromboembolism risk [7,19–21]. These findings supported the feasibility of functional exercises for gynecologic patients. Despite these findings, however, a small randomized study found that active toe movement was not a viable strategy for thromboprophylaxis in patients with acute foot and ankle trauma treated with cast immobilization [22]. In our report, a regular, comprehensive pattern of exercise under the instruction and supervision from medical staff could indeed decrease the risk of venous thrombosis. However, the definite value of exercise on the prevention of VTE needs a larger patient population to confirm. Considering the safe, feasible and low-cost aspects of these functional exercises, it is worth generalizing to almost all gynecologic patients.

In our trial, the universal patient education apparently played an important role in the prevention of DVT, as the patients had a more accurate perception of DVT. Compared with the prevalence of DVT in patients with gynecologic cancer in previous reports [3,4], both the study and control group had fewer instances of DVT and no PE. There are numerous studies supporting the important role of education in VTE prevention, as teaching patients the importance of recognizing VTE signs and preventive/survival skills is potentially lifesaving [23]. A cohort study revealed that the provision of targeted written and verbal educational information during the preoperative assessment was an effective method of increasing a patient's awareness of these topics. Increased patient awareness may empower patients in their post-operative recovery and enable them to make more informed decisions regarding VTE prophylaxis options [24]. Various strategies and tools are available to help physicians establish good VTE practices, among which educational programs are an important component [25]. These programs or protocols have included a multifaceted intervention with an alert [26], rounds with multidisciplinary surgical teams [27], nurse-initiated preoperational education and counseling [28], and an education program together with the use of a sticker [29]. Education for nurses significantly improved medication administration practices for venous thromboembolism prevention [30]. A VTE educational video can be an effective tool for improving patient knowledge of the condition [31]. Online education on the topic of VTE prophylaxis concepts has been used [32]. Most of these ideas had been integrated into our study design and contributed to a high level of patient satisfaction and acceptance.

Very studies concentrated on the subjects of intramuscular venous thrombosis in cancer surgeries. In a trial of intertrochanteric fracture, intramuscular thrombosis occurred in 9/51 and 2/45 patients of control and test groups respectively, [33] which were similar with the situations in our study. It is possible that, even in the absence of more proximal involvement, intramuscular calf thrombosis may be associated with pulmonary embolism [34]. Hence, the prevention of intramuscular thrombosis is also very important for patients with major surgeries. Intramuscular venous thrombosis can present as marked edema-like muscle changes on MRI [35]. However, in our study the ultrasound provided an inexpensive and convenient method of diagnosis.

There are several limitations in our study. As some subtypes of ovarian cancer cause a higher risk of VTE, [36] detailed pathological analysis is essential for a large population. Due to the sample size limitation, we could not draw any conclusion about the effects of exercises on the prevention of VTE. Autar scale does not include gynecological surgery in previous reports, which is an important limitation of the generalization of our findings. Although there were no studies compared the efficacy of risk predicting tools for thrombosis prevention, a Caprini score model would probably provide diverse risk stratification of thrombosis in the study population [37,38]. It should be kept in mind that other potential risk factors, such as post-operative infections, would increase the risk of venous infections. Therefore, a comprehensive description of peri-operative complications had better be provided to clarify such problems. Due to limited size of thrombosis events and heterogeneity of the cancers, we couldn't introduce a cut-off of D-dimer for prediction, although patients with venous thrombosis had significantly higher D-dimer values. Last but the most important, we could not differentiate the role of deep breathing and lower limb motions in the prevention of venous thrombosis. These issues require a larger, stratified cohort or randomized study to validate.

5. Conclusions

In a phase 3 single-center randomized controlled study, a comprehensive set of functional exercises combining deep breathing and lower limb motions would significantly decrease the risk of venous thrombosis in patients undergoing major surgery for gynecologic malignancy, especially the risk of intramuscular thrombosis. Simultaneously, a thoughtful patient education program would improve the patient's perception about the prevention of VTE and their satisfaction.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.04.013.

Statement of IRB approval

The Institutional Review Board of Peking Union Medical College Hospital has approved this study (No. JS-1690). The registration No. is NCT03740633 (*clinicaltrials.gov*).

Study design

Phase 3 randomized controlled study.

Statement

The paper is not under consideration at another journal, and no previous presentations and/or publications have been using the same material in this paper.

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Disclosure

All authors declare that they have no conflicts of interest to disclose.

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