

The incidence and risk factors of venous thromboembolism following elective gynecological surgeries without systemic thromboprophylaxis - an observational cohort study in a Chinese tertiary hospital

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Summary

Purpose of investigation: To investigate the incidence and risk factors of venous thromboembolism (VTE) after gynecological surgery without systemic thromboprophylaxis. **Materials and Methods:** Consecutive adult Chinese medical patients not receiving pharmacological or systemic mechanical prophylaxis for VTE before elective gynecological surgery. An observational cohort study of 620 patients in a gynecological department in a Chinese tertiary hospital. **Results:** Lower extremity deep venous thrombosis was detected by ultrasound examination in 57 (9.19%) of the patients, 39 had computed tomography pulmonary angiography (CTPA) evaluation after being diagnosed with lower extremity deep venous thrombosis (LEDVT), and the diagnosis was confirmed in 18 subjects, resulting in a pulmonary embolism (PE) incidence of 46.2% among the 39 patients, and 13 (72.2%) were asymptomatic and without significant clinical features. **Conclusions:** In the absence of pharmacological or systemic mechanical prophylaxis, gynecological surgeries carried a significant risk for VTE in the Chinese study population. As clinical features are not able to reliably exclude the presence of PE, early routine prophylaxis is warranted based on risk factors in postoperative gynecological patients and should strongly be considered.

Key words: Venous thromboembolism (VTE); Pulmonary embolism (PE); Gynecological surgery.

Introduction

Thromboembolism, especially pulmonary embolism (PE), is regarded as one of the most common life-threatening complications, and usually results from lower extremity deep venous thrombosis (LEDVT) [1-3] after abdominal and pelvic surgery.

The statistics are alarming, especially considering that even distal calf thrombi have the ability to propagate proximally and cause catastrophic complications, such as massive PE and death. The overall incidence of LEDVT without prophylaxis is 17% to 40% for patients undergoing gynecological surgery [3-6]. The incidence of PE after gynecological surgery ranges from 0.3% to 0.8%. However, the incidence of asymptomatic PE in all surgeries is reported to be as high as 50% or more [7].

The ultrasound scan has become routine in screening silent LEDVT, and computed tomography pulmonary angiography (CTPA) has widely been accepted as a good method for the evaluation of pulmonary embolism [8-10] that makes it feasible to find the PE at an earlier stage and improves the prognosis after gynecological surgery.

However, the incidence of venous thromboembolism (VTE) in the Chinese population was believed to be rare

due to poor understanding of the disease and limited evidence. In this background of poor understanding of VTE incidence, and risk factors in the Chinese population after gynecological surgery, and concerns over the bleeding complications from pharmacological prophylaxis, a systemic thromboprophylactic strategy for the Chinese population was not established and widely implemented at the time of this study. The primary objectives of this observational cohort study were to investigate the incidence and risk factors of VTE for patients undergoing gynecological surgery in a typical Chinese tertiary hospital without pharmacological or systemic mechanical thromboprophylaxis, and to provide the basis for the development and implementation of a cost-effective systemic thromboprophylactic strategy for the Chinese population.

Materials and Methods

Between May 2007 to December 2008, 620 consecutive adult Chinese patients aged 18 years or older, who were undergoing elective pelvic gynecological surgery in the Department of Gynecology, Beijing Chao-yang Hospital Affiliated with Capital Medical University, were recruited. Informed consent was obtained from every patient included in the study. Concomitant treat-

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Table 1. — Perioperative demographic characteristics of the VTE and non-VTE groups

Risk factors	VTE (n=57)	Non-VTE (n=563)	OR (95% CI)
Demographic characteristics			
Age (years) (<i>M</i> (IQR))	59.14 (35–83)	45.83 (16–82)	
Age ≥ 60 years (n (%))	31 (54.4%)	88 (15.6%)	6.44 (3.64–11.37)
BMI (<i>M</i> (IQR))	25.25 (18.05–38.05)	23.98 (15.94–39.57)	
Malignant case (n (%))	31 (54.4%)	65 (11.5%)	4.57 (3.29–6.34)
Comorbidities (n (%))			
Hypertension	10 (17.5%)	27 (4.8%)	4.22 (1.93–9.26)
Diabetes	23 (40.4%)	83 (14.7%)	5.54 (2.99–10.28)
Other comorbidities	7 (12.3%)	36 (6.4%)	2.05 (0.87–4.84)
Operative factors			
Operative route (lap/TVS/TA)	14/7/36	333/59/171	
Operation type (minor/major*)	26/31	509/54	
Total operation time (h) (<i>M</i> (IQR))	3.38 (1–11.5)	2.08 (0.3–8)	
Operation time ≥ 2.5 hours (n (%))	37 (64.9%)	160 (28.4%)	4.66 (2.63–8.27)
Total operational blood loss (ml) (<i>M</i> (IQR))	260 (5–1500)	113 (0–2500)	
Operational blood loss ≥ 400ml (n (%))	14 (24.6%)	41 (7.3%)	4.15 (2.09–8.20)
General/non-general anesthesia	52/5	476/87	1.9 (0.74–4.89)
Postoperative factors			
Total postoperative immobilization time (hours) (<i>M</i> (IQR))	55.9 (24–168)	32.3 (12–120)	
Postoperative immobilization time ≥ 48 hours (n (%))	36 (63.2%)	106 (18.8%)	7.39 (4.15–13.18)

VTE: venous thromboembolism; OR: odds ratio; CI: confidence interval; IQR: Inter-quartile range; BMI: body mass index; lap: laparoscopic surgery; TVS: transvaginal surgery; TA: transabdominal surgery.

ment with aspirin or other anticoagulation agents was not permitted during the study. Patients with a past history of VTE and pregnant subjects were excluded from the study.

Neither chemoprophylaxis nor systemic mechanical methods against VTE, such as conventional and standard intermittent pneumatic compression, were employed in the perioperative period. Non-systemic thromboprophylactic measures were utilized, including encouraging early lower extremity movement in bed or early ambulation postoperatively, and substandard employment of compression stockings. The intensity and duration of the non-systemic thromboprophylactic therapy were limited and not collected in detail during this study.

All patients' perioperative demographic characteristics were collected, and each enrolled patient received baseline venous duplex investigations of both lower limbs within one week prior to the operation and at least twice postoperatively, once on postoperative day 2 and once during days 5 to 7. If any of these scans revealed the presence of LEDVT, a follow-up CT pulmonary angiography scan was arranged within 72 hours, and CTPA was also performed on those with suggestive VTE and PE findings.

Suggestive signs and symptoms of LEDVT included calf pain or tenderness, increased skin warmth, swelling, decreased calf ballotability, increased calf circumference, and positive Homan's sign. The clinical findings that suggested PE included dyspnea, chest pain, tachycardia, abnormal arterial blood gases (acute respiratory alkalosis, hypocapnia, and hypoxemia), electrocardiogram (ECG) findings (presence of a classic S1 Q3 T3 pattern with or without a right bundle branch block pattern), and pulmonary hypertension in the echocardiogram as part of the evaluation collected pre- and postoperatively.

Demographic and preoperative data, operative time, and postoperative complications were all recorded for analysis using a structured proforma. All continuous variables were expressed as means and standard deviations. Continuous variables were analyzed by Student's *t*-test, categorical data by Fisher's exact test, and multiple variables by logistic regression. Data analysis was

performed with SPSS version 15.0 and differences with a *p*-value less than 0.05 were regarded as statistically significant. All patients received standard anti-thromboembolism treatment after DVT or PE confirmation, and there were no mortalities, but the individual regimen and outcomes were not recorded in this study.

Results

From the 620 patients enrolled in this observational study, LEDVT was determined postoperatively in 57 cases (9.19%) by ultrasound screening. Because a PE needed to be ruled out, further CTPA investigation was offered to these patients. The perioperative demographic characteristics of the VTE and non-VTE groups are shown in detail in Table 1. Multivariate analysis identified only older age (OR=1.066), malignancy (OR=10.79), operation type (OR=6.47), and duration of immobilization (OR=1.061) to be significant.

Among the 57 VTE cases, 39 patients had CTPA performed two days after being diagnosed with LEDVT by ultrasound. Unfortunately, 15 patients could not receive the scan due to contrast anaphylaxis or other contraindications, and three declined for personal reasons. From the limited radiological examinations, 18 PE cases were confirmed. However, among the 39 patients, there were no statistically significant differences in terms of risk factors between the PE and non-PE groups.

For the positive scan cases, the location of the PE was stratified into left and/or right main, lobar, or segmental arteries, and classified as single or multiple. Only the largest vessel order clot was noted for each side, yielding two main,

Table 2. — Statistically significant *p*-values* for risk factors and clinical variables stratified by clot number and location of PE.

	Main Single/multiple	Lobar Single/multiple	Segmental Single/multiple
Risk factors			
Older age**	0.288/1.000	0.929/0.215	0.552/0.462
Malignancy	0.284/1.000	0.243/0.447	1.000/1.000
Extensive procedure	0.239/1.000	0.668/0.426	1.000/1.000
Longer immobilization time	0.405/1.000	0.276/0.100	0.531/0.158
Symptoms and clinical variables			
Dyspnea	0.339/1.000	0.668/0.426	1.000/1.000
Tachycardia	0.453/1.000	0.735/0.531	0.317/0.315
Chest pain	0.608/1.000	0.817/0.668	0.496/0.171
Syncope	0.608/1.000	0.817/0.668	0.496/0.171
SpO ₂ < 95% or PO ₂ < 60 mmHg	0.896/1.000	0.551/0.872	0.729/0.729
ECG(+)	0.453/1.000	0.735/0.531	0.317/0.317
Echocardiogram (+)	0.637/1.000	0.668/0.426	0.201/0.201

*Statistical analysis was performed by a medical statistician using an independent samples *t*-test with a two-tailed *p* value. Significance was defined as a *p* value less than 0.05. **Age ≥ 60 years. PE: pulmonary embolism; SpO₂: pulse oxygen saturation; PO₂: partial pressure of oxygen; ECG: electrocardiogram.

12 lobar, and 32 segmental clots. Dyspnea, tachycardia, syncope, and chest pain were noted as positive clinical findings in the postoperative observation period. Among the PE cases, dyspnea was the most common significant symptom (4/18, 22.2%), and occurred concurrently, offering more specificity, with tachycardia (2/18, 11.1%), chest pain (1/18, 5.6%), and syncope (1/18, 5.6%) ($p < 0.05$), but 72.2% of the PE patients were asymptomatic. An ABG abnormality was the most common ancillary test finding (5/18, 27.8%), marked by hypoxemia (SpO₂ < 95% or PO₂ < 60 mmHg), and was followed by unspecified echocardiogram and ECG changes (3/18, 16.7%; and 2/18, 11.1%, respectively). There were no significant findings either for the risk factors or the symptoms of syncope, tachycardia, chest pain, dyspnea, and other clinical variables in respect to specific clot locations. Risk factors and clinical symptoms were correlated with scan results (positive vs. negative) and with the precise location of PE, as presented in Table 2.

Discussion

According to Edition 8 of the American College of Chest Physicians (ACCP) Guidelines, the incidence of asymptomatic VTE based on objective diagnostic screening is 15–40% among patients undergoing major gynecologic surgery without preventive measures, which is comparable to those of general surgery, major urological operations, and neurosurgery [11]. The PE prevalence in Asian countries are reported to be significantly high at three to four per 10,000 surgeries [12], and the gynecological postoperative PE incidence is reported to range from 2.41% to greater than 3% in a recent study [13]. The incidence of postoperative VTE in the Chinese population was believed to be rare due to poor understanding of the disease and lim-

ited evidence, especially in gynecological surgery [14–16]. The present study indicates a high incidence of 9.2% of LEDVT and approximately 4–5% of PE among the 620 enrolled patients. This result is comparable to the reported prevalence in the ACCP guidelines. Similar to a pilot study in the same hospital of 141 post-gynecological pelvic surgery patients that reveals an extraordinarily high LEDVT incidence [17], the present study also demonstrates a remarkably high incidence in an even larger patient population. Therefore, this research calls into question future study protocols that do not utilize pharmacological or systemic mechanical thromboembolic prophylaxis in China. In this study, 40–50% of detected LEDVT patients had a confirmed PE, and most LEDVT cases were silent. The strong relationship between LEDVT and PE suggests that postoperative thromboembolism is one disorder rather than two separate conditions or courses, a concept that is supported by increasing evidence in recent years [11].

It is of great importance to predict which individuals will develop a clinically significant thromboembolism. Published research investigating postoperative PE after gynecologic surgery has identified several risk factors based on univariate logistic regressions, including older age, previous VTE, malignancy, immobilization, and operative factors [8]. The present study found that age over 60 years, a major operation, prolonged immobilization time over 48 hours, and malignancy were significant risk factors of VTE after gynecologic surgery based on multivariate analyses. Among these risk factors, malignancy (OR = 10.79) and operation type (OR = 6.47) were the most prominent. Malignancy is frequently reported as an independent risk factor of VTE [8, 18, 19].

Additional studies also reveal that malignancy is a risk factor of PE in gynecologic surgery [20, 21]. In the present

study, malignancy was consistently associated with extensive operative procedures, including radical hysterectomy, systemic lymphadenectomy, and pelvic exenteration. Malignancy likely compounds the risk for thromboembolism during extensive procedures. Therefore, the presence of a malignant tumor is a very important and strong risk factor for VTE and PE.

Because of less specific and sensitive initial clinical features, PE is considered to be a diagnostic challenge for the physician [22, 23], and most tend to be biased toward symptomatic cases. PE may be asymptomatic or associated with little significant clinical symptoms or variable changes, but when an embolus becomes extensive, it can produce a fatal clinical manifestation [24]. Patients' symptoms can vary based on their respiratory and cardiopulmonary reserve, pain tolerance, size of the clot, and the presence or absence of pulmonary infarction. In the present study, there were no symptoms or clinical features that were significantly associated with a positive scan. Several previous studies have suggested that the location and size of the PE clot would correlate with the clinical manifestations [22, 25, 26]. The present results did not demonstrate this to be the case, suggesting that the size and location of PE cannot be predicted by the clinical presentation or the presence of risk factors in patients undergoing gynecological surgery. Although risk factors, symptoms, and clinical features were associated with thromboembolism, they did not associate with the location of the clot. This suggests that the severity of PE may have no definitive relationship with the clinical manifestations and risk factors, and reveals that pulmonary embolization is a very complicated pathophysiological process.

The thromboprophylaxis and treatment strategy should ideally be based on the diagnosis of a PE. Unfortunately, neither the patients' clinical status nor medical history can predict a PE condition promptly and exactly. Because clinical presentation is unreliable for diagnosis, imaging modalities have become the most effective way to diagnose a PE. CT pulmonary angiography is currently considered the gold standard for diagnosing a PE [27]. It allows the clear and direct visualization of the pulmonary vasculature, and also can reliably detect alternative or additional conditions with a high specificity and sensitivity. However, CTPA is limited in the imaging quality of subsegmental arteries, is relatively less economical compared to VQ scans, exposes the patients to radiation and intravenous contrast agents, and can lead to unnecessary over-treatment of certain individuals [28].

Due to the limitation of historical background, some patients with high thromboembolism risk factors did not receive proper prophylaxis in this observational study. Nevertheless, when this study was terminated by the local Ethical Committee after a high incidence of thromboembolism was demonstrated, a prophylactic study was initiated immediately based on the current consensus and data

from this study. Those patients with high thromboembolism risk and other perioperative factors received pharmacological or systemic mechanical prophylaxis in the hospital. The prophylactic study is currently on-going in the center.

Conclusion

The present data demonstrated that the incidence of VTE is relatively high after gynecological surgery without chemoprophylaxis or systemic mechanical prophylaxis in a typical Chinese tertiary hospital. VTE frequency was higher in the cases that had risk factors, such as older age, malignancy, non-laparoscopic procedures, and longer immobilization time. Among the VTE cases, PE prevalence is remarkable for having atypical and non-specific clinical presentations, and the size and location of PE were inconsistent with these clinical presentations, which indicates that the diagnosis cannot depend on clinical manifestations, and that the prevention strategy should be based on risk factors.

Thromboembolic complications, especially PE, after gynecological surgery, cause significant morbidity and mortality for patients. It is imperative that an effective thromboembolic prophylactic strategy is established based on sufficient evidence. This study should increase the awareness of VTE and especially PE after pelvic gynecological operations. In addition to the Chinese population, caution should be taken and systemic preventive measures should be considered in all pelvic gynecological surgical patients. Further studies are needed to solve the challenging diagnostic problem that PE poses in developing an effective and efficient method for treating these conditions early in order to minimize the significant morbidity and mortality associated with gynecological surgery in the Chinese population.

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