Perioperative Venous Thromboembolism in Patients with Gynecological Malignancies: A Lesson from Four Years of Recent Clinical Experience

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Abstract. *Aim: To analyze clinical characteristics of venous thromboembolisms (VTE) in gynecological malignancies, and to find a cost-effective prophylaxis procedure for post-operative VTE. Patients and Methods: We analyzed clinical characteristics of 751 patients who underwent definitive surgery for gynecologic malignancies, and cost-effectiveness of VTE prophylaxis. Results: VTE was diagnosed preoperatively in 4.5% of ovarian cancer cases, more frequently than any other type ($p<0.005$). Older age and greater length of operation were independent risk factors for postoperative VTE. To prevent eight VTEs in 738 malignant cases, which occurred during day 2 to 10, $617,783, $726,185, or $994,222 were necessary for continuous VTE prophylaxis, using either unfractionated heparin (UFH), low-molecular weight heparin or fondaparinux, respectively. Conclusion: A strategy which might be cost-effective for post-surgical management of gynecological malignances is use of UFH three times combined with graduated compression stockings and intermittent pneumatic compression, thorough SpO_2 monitoring, and perioperative measurements of the circumference of both sides of thighs and calves.*

Patients undergoing pelvic or abdominal surgery for gynecologic malignancies are at high risk of a postoperative venous thromboembolism (VTE), including a deep-vein thrombosis (DVT) or a pulmonary embolism (PE). The postoperative VTE risk in patients with ovarian cancer has been reported to be as high as 39% (1-7).

Intermittent pneumatic compression (IPC), unfractionated heparin (UFH), low-molecular weight heparin (LMWH), and a new anti-coagulant, the synthetic factor Xa inhibitor fondaparinux, which does not bind to thrombin, have all been used to prevent postoperative VTE in gynecologic cancer patients. Clarke-Pearson *et al*. reported that IPC combined with graduated compression stockings (GCS) significantly reduced the incidence of postoperative VTE (8). In a meta-analysis of 10 different trials, UFH prophylaxis alone was shown to reduce DVT rates from 30.6% to 13.6% (9). In another meta-analysis, LMWH was demonstrated to be as safe and effective as UFH in reducing VTE in patients with cancer, without increasing bleeding complications (10). Recently, postoperative fondaparinux administration was demonstrated to be at least as effective as LMWH in patients undergoing high-risk abdominal surgery (11).

However, the appropriate duration for VTE prophylaxis for each of these different methodologies is not clear. The range of recommended UFH, LMWH, or fondaparinux treatments varies from 1-5 weeks (12-14). In practice, the majority of such prophylactic regimens are approximately 10 days in duration; however, it is possible that patients at highest risk for VTE, such as those undergoing cancer surgeries, may benefit from an extended prophylactic regimen. In fact, the National Comprehensive Cancer Network guidelines recommend a continuation of prophylaxis well after hospital discharge in high-risk patients with cancer undergoing surgery (15). In order to determine the most appropriate duration for VTE prophylaxis, the time/distribution of occurrence of VTE cases is an important issue to be analyzed; however, there have only been surprisingly few such studies, and these present relatively different data (16, 17).

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Okadome *et al*. analyzed a susceptibility period of VTE only for pulmonary embolisms (PE). All postoperative PEs in their study were clinically detected within nine days from surgery, including both malignant and benign gynecological tumors, and found the highest frequency occurred on the second day (17). In another retrospective study, although 76% of VTE cases were diagnosed between eight and 90 days from surgery, the maximum number of cases also occurred during the first week(16).

Another important point to consider for determining the appropriate duration of VTE prophylaxis is the cost-effectiveness of any such treatment. Teoh *et al*. conducted an economic analysis of VTE prophylaxis. They estimated the incidence of VTE, bleeding, and heparin-induced thrombocytopenia (HIT) was 5.4%, 5%, and 2.6%, respectively, under prophylaxis by UFH, and 5.9%, 4.8%, and 0.2%, respectively, under prophylaxis with LMWH (7). The costs for prophylactic UFH and LMWH for 10 days were estimated to be $407 and $983, respectively. The charge for prophylactic fondaparinux for 10 days was estimated using the comparative costs of fondaparinux and LMWH (enoxaparin) (18). The charges for VTE treatment by LMWH and warfarin were $24,350 and $1,234, respectively, and those for bleeding treatment and HIT treatment were $1,068 and $15,497, respectively (7).

In the present study, we analyzed the period of susceptibility for post-surgical VTE cases at our center that received a shortened duration of prophylactic procedure of GCS, IPC, and UFH. We then performed an economic comparison between our short-term strategy of VTE prophylaxis and that combined with an extended duration of UFH, additional LMWH, or additional fondaparinux.

Patients and Methods

During the 2007 to 2010 study period, 751 patients with gynecological malignancies underwent definitive surgery at Department of Obstetrics and Gynecology at Osaka University Hospital, Osaka, Japan. We excluded those patients who only underwent biopsy. All patients received preoperative DVT screening by comparative measurement of the circumference of both side of their thighs and calves, as well as a clinical examination for Homan's sign by palpation. DVT was suspected if the laterality in circumference of either thighs or calves was equal to or larger than 2 cm; DVT was confirmed using ultrasonography. All patients also received chest multidetector-row computed tomography (MDCT) screening for pulmonary metastasis and PE. The SpO_2 baseline level was measured preoperatively.

For those diagnosed with preoperative VTE, UDH and warfarin were immediately introduced therapeutically. For those who were negative for VTE, the prophylaxis for VTE was performed usually by use of GCS and IPC, with addition of UFH. UFH was subcutaneously administered three times: 2,500 IU at 2 h preoperatively and 5,000 IU at 2 h and 14 h postoperatively. SpO_2 was continuously measured following the surgery until the patient finished her first walk on the first day (day 1). After the first walk, SpO_2 was measured at least twice on the day 1 and at least once on day 2, but was not measured routinely thereafter.

We first analyzed the incidence and timing of pre- and postoperatively diagnosed VTE cases. Next, the symptoms, risk factors and time of susceptibility of VTE, especially in the post-operative cases were analyzed. We conducted an economical comparison of prophylaxis methods only for cases without perioperative VTE. Our short-duration strategy using GCS and IPC with three administrations of UFH was compared with a 10-day strategy using UFH, LMWH or fondaparinux (which is the procedure usually performed in western countries). In this evaluation, UFH, LMWH and fondaparinux were purported to be highly effective for VTE prophylaxis, and the number of VTEs during day 2 to day 10 was expected to be zero. The bleeding risk associated with fondaparinux was presumed to be the same as that of LMWH. HIT was not expected in patients who received fondaparinux.

Statistical analysis. MedCalc (MedCalc Software, Mariakerke, Belgium) was used for statistical analysis. The site of tumor origin and susceptibility for VTE was analyzed by the chi-square test. Multivariate Cox proportional hazards model (step-wise method) for characteristics of these patients, including age, body mass index (BMI), origin of the malignant tumor, operation time and blood loss, were calculated to find independent risk factors. Results were considered to be significant when the p-value was less than 0.05.

Statements of ethics. This study was approved by the Institutional Review Board and the Ethics Committee of the Osaka University Hospital. All patients provided written informed consent (approval of this analysis: #10302; approved on March 11, 2011).

Results

Clinical characteristics of the VTE cases. Among the 751 patients with gynecological malignancies who underwent definitive surgery, VTE was diagnosed preoperatively in 13 (1.7%) and postoperatively in 28 cases (3.7%) (Table I). In the preoperatively diagnosed cases, 4.5% of ovarian cancer cases exhibited VTE. This frequency was significantly higher than 0.5% for cervical cancer, 0.3% for endometrial cancer, and 1.7% of the other cases ($p<0.005$ by Chi-square test). On the other hand, no significant difference was detected in the origin of the tumors for postoperatively diagnosed VTEs ($p=0.42$ by chi-square test). The preoperatively-diagnosed VTE cases were excluded from further analysis.

Seven hundred and thirty-eight patients who were negative for preoperative VTE underwent surgery while under prophylaxis by GCS and IPC, with or without UFH. As for prophylaxis of VTE, 180 patients (24%) underwent only use of GCS and IPC; however, the other 571 patients (76%) underwent surgery with UFH, GCS and IPC. The median age was 56 (range=25-87) years and the median BMI of these patients was 21.9 (range=13.8-50.2). The different origins of the malignant tumors was: the uterine cervix in 191 patients (26%), the endometrium in 286 patients (39%), the

Table I. *Incidence of preoperative and postoperative venous thromboembolism (VTE) in gynecological malignancies. VTE was detected preoperatively in 4.5% of ovarian cancer cases. This frequency was significantly higher than that of cancer of other origins (p<0.005 by chi-square test).*

Tumor origin	Preoperative	Postoperative*
Uterine cervix	1/192 (0.5%)	8/191 (4.2%)
Uterine corpus**	1/287 (0.3%)	8/286 (2.8%)
Ovary**, ***	11/266 (4.1%)****	12/255 (4.7%)
Others	0/9 (0.0%)	0/9 (0.0%)
Total	13/751 (1.7%)	28/738 (3.8%)

*Excluding preoperatively diagnosed VTE cases; **including three cases of concurrent corpus and ovarian cancer; ***including 16 cases of peritoneal cancer and four cases of tubular cancer; ****$p<0.005$ by Chi-square test.

Table II. *Symptoms of venous thromboembolism (VTE). The presenting symptoms of the patients at the time of diagnosis of VTE are listed.*

Symptom	Number of cases
DVT alone	6
Leg swelling	4
Fever	1
Other	1
None (asymptomatic)	0
PE alone or DVT+PE	22
Dyspnea	2
Nausea	2
Others	3
None (asymptomatic)	15 All had decreased SpO_2

DVT: Deep-vein thrombosis; PE: pulmonary embolism.

ovary/fallopian tube/peritoneum in 255 patients (35%), and other or unknown organs in nine patients (1.2%). Three patients suffered from double cancer of the endometrium and the ovary.

Among these 738 patients, 580 (77%) were diagnosed with stage I or II tumors, and the remaining 171 cases (23%) with stage III or IV. Pelvic lymphadenectomy was performed in 570 cases (76%), and para-aortic lymphadenectomy in 243 cases (32%). The median operative time was 310 (range=50-925) min and the median blood loss was 630 ml (range=10-100 ml). Transfusion, including auto-transfusion, was performed in 202 cases (27%).

Symptoms of VTE. Among 28 postoperative VTE cases, six (21%) exhibited DVT alone, nine (32%) PE alone, and both DVT and PE were observed in the remaining 13 cases (46%). The symptoms of these patients at diagnosis of VTE are listed in Table II. Four (67%) of the six patients with DVT complained of leg swelling; however, 15 (68%) of the patients with PE, with or without DVT, had no complaint of any symptoms, although all of them clinically demonstrated decreased SpO_2.

Risk factors of VTE. Multivariate Cox proportional hazards analysis for the risk factors for VTE, including age, BMI, tumor origin, operation time and blood loss, was performed (Table III). Among these factors, a multivariate analysis showed that age (>60 years old) and operative time (>360 minutes) were significant independent factors for VTE risk. The adjusted HR for VTE (without *versus* with) was 4.4314 (95% confidence interval (CI)=1.6861-11.6464, $p=0.0025$) and 3.6698 (95% CI=1.2186-11.0512, $p=0.021$), respectively.

Table III. *Risk factors for venous thromboembolism (VTE). Multivariate Cox proportional hazards analyses (step-wise method) for factors including age, body mass index (BMI) of these patients, origin of the malignant tumors, operation time, and blood loss were performed.*

Variable	Adjusted HR	95% CI	*p*-Value
Age (years)		1.6861-11.6464	0.0025
≤60	1		
>60	4.4314		
BMI		0.5970-3.8755	
≤23	1		0.38
>24	1.5210		
Tumor origin		0.5385-3.8285	
Non-ovarian	1		0.47
Ovarian*	1.4359		
Operation time (min)		1.2186-11.0512	
≤360	1		0.021
>360	3.6698		
Blood loss (ml)		0.2809-2.7128	
≤1000	1		0.81
>1000	0.8729		

*Including tumors of the fallopian tube and peritoneum. BMI: Body mass index; HR: hazard ratio; CI: confidence interval.

Time of susceptibility to postoperative VTE. In 19 (68%) out of the 28 postoperative VTE cases, VTE was diagnosed on the first day after surgery, 13 (68%) of whom developed VTE during their first walk (Figure 1). At our Hospital, we did not usually administer UFH after the first walk, and the patients were encouraged to move and walk. VTE was detected in only eight cases (29%) between day 2 and 10, the time period during which VTE prophylaxis normally performed in most Western countries. Out of these eight cases, a PE was diagnosed in only three; two on the second day and one on the 14th day. *Economical comparison between our short-duration*

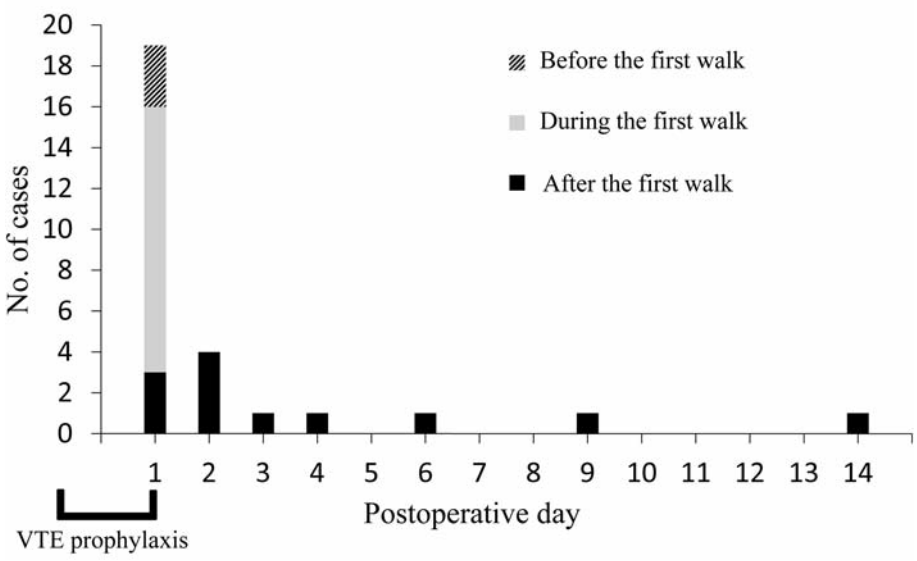

Figure 1. *Time of susceptibility to postoperative venous thromboembolism (VTE).*

strategy and a 10-day strategy for VTE prophylaxis. Teoh *et al*. evaluated the costs and effectiveness of VTE prophylaxis strategies following laparotomy for ovarian cancer (7). They calculated the charges for 10 days of IPC, in-patient UFH or in-patient LMWH, to be \$245, \$407 and \$983, respectively. VTE treatments using LMWH or warfarin were estimated to be \$24,348 or \$1,232, respectively. The bleeding and HIT risks of UFH were estimated to 5% and 2.6%, those of LMWH were 4.8% and 0.2%. The costs for bleeding treatment and HIT treatment were also estimated to be \$1,068 and \$15,497, respectively. For estimation of the prophylaxis costs using fondaparinux, we calculated the cost of 10 days of in-patient fondaparinux to be 1.58 (£3.58/£2.26) times as much as that of LMWH (enoxaparin), based on the baseline daily cost of fondaparinux and enoxaparin (18).

In the present study, 19 out of 28 VTE cases occurred on day 1, however VTE prophylaxis was performed. We conjecture that the efficacy of VTE prevention was equal among UFH, LMWH and fondaparinux. We estimated the additional cost of a strategy with additional UFH, LMWH or fondaparinux from day 2 to 10 after routine three perioperative UFH administrations, and compared these costs to that of a strategy of three perioperative UFH administrations alone (Table IV).

Under this scenario, our strategy of three perioperative UFH administrations failed to prevent eight VTEs during day 2 to 10, and \$9,856 was necessary for VTE treatment using warfarin, or \$19,4784 was necessary using LMWH. On the other hand, for continuous VTE prophylaxis using UFH, LWMH or fondaparinux, \$617,783, \$726,185, or \$994,222, respectively, was necessary.

Discussion

Patients undergoing pelvic and abdominal surgery for gynecological malignancies are at high risk of venous thromboembolisms, including DVT and PE. The postoperative VTE risk in patients with ovarian cancer has been reported to be as high as 39% (1-7). Cytoreductive surgery was usually performed for the ovarian carcinoma cases. Similarly, cytoreductive surgery was also shown to be effective for advanced endometrial carcinomas (19). Postoperative VTE is one of the problems for such cases.

The present study found that the incidence of preoperative VTE was significantly higher in patients with ovarian carcinomas, including tubal and peritoneal carcinoma cases, than for other malignancies ($p<0.005$ by the Chi-square test), showing that an ovarian carcinoma could trigger a VTE even before any surgery was performed. Seven hundred and thirty-eight patients who were negative for preoperative VTE underwent definitive surgery, under prophylaxis by GCS and IPC, mostly with, or partly without, UFH. When given, the UFH was subcutaneously administered three times: 2,500 IU 2 h preoperatively and 5,000 IU 2 hours (day 0) and 14 h postoperatively (day 1). Our previous study showed that prophylactic administration of 2,500 IU UFH was sufficiently effective for our Japanese ethnic population (20). Under this prophylaxis, postoperative VTE was detected in 28 cases, including six (21%) with DVT alone, nine (32%) with PE alone, and 13 cases (46%) exhibiting both DVT and PE. Fifteen (68%) out of 22 patients with PE, with or without DVT, did not complain of any symptoms, and demonstrated decreased SpO_2, implying the significance of

Table IV. *Economics comparison of venous thromboembolism (VTE) prophylaxis between our two-day short-duration strategy and a typical western 10-day strategy. We evaluated the estimated additional cost of a strategy in which unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux was used from day 2 to day 10, compared to that of our short-duration strategy of postoperative VTE prophylaxis using graduated compression stockings and intermittent pneumatic compression with three administrations of UFH at our hospital. The Baseline Cost was referenced from previous studies conducted by Teoh et al. (7) and Gordois et al. (18). In this evaluation, UFH, LMWH and fondaparinux were purported to be highly effective for VTE prophylaxis, and the number of VTEs during day 2 to day 10 was expected to be zero. The bleeding risk for fondaparinux was supposed to be the same as that of LMWH. No heparin-induced thrombocytopenia was expected in patients who received fondaparinux.*

Prophylaxis	VTE during day 2-10	VTE-related death	Estimated additional cost	
UFH until the first walk	8 (PE: 2)	0	VTE treatment with warfarin	\$1232×8=\$9,856 (\$13/person)
			or	
			VTE treatment with LMWH	\$24348×8=\$194,784 (\$259/person)
UFH until day 10	0 (supposed)	0 (supposed)	Inpatient UFH	\$407×9/10×751=\$275,091
			Bleeding treatment	\$1,068×751×5%=\$40,103
			HIT treatment	\$1,5497×751×2.6%=\$302,594
			Total	\$617,788 (\$823/person)
LMWH until day 10	0 (supposed)	0 (supposed)	Inpatient LMWH	\$983×9/10×751=\$664,410
			Bleeding treatment	\$1,068×751×4.8%=\$38,499
			HIT treatment	\$15,497×751×0.2%=\$23,276
			Total	\$726,185 (\$967/person)
Fondaparinux until day 10	0 (supposed)	0 (supposed)	Inpatient fondaparinux	\$1,414×9/10×751=\$95,5723
			Bleeding treatment	\$1,068×751×4.8%=\$38,499
			Total	\$994,222 (\$1,324/person)

continuous SpO_2 monitoring. There were no deaths due to VTE. Multivariate analysis of risk factors for postoperative VTE showed that patients' age and operative time were significantly important factors. These results were consistent with a previous report (17).

In order to determine an appropriate duration of VTE prophylaxis, the time of incidence distribution of VTE cases should be an important issue for analysis. Under our strategy of prophylaxis, 19 (68%) out of 28 postoperative VTEs were diagnosed on day 1. VTE was detected in only eight cases (29%) between day 2 and 10, the period when VTE prophylaxis is typically performed in western countries. In these eight cases, PE was diagnosed in three: two on the second day and one on the 14th day, and there was no death.

There have been only a few studies reporting the time of susceptibility for VTE in gynecological surgery (16, 17). Okadome *et al*. analyzed only PE cases, all of which were clinically detected within nine days from surgery for gynecological diseases (including both malignant and benign tumors), with the highest frequency of VTE on the second day (17). In their study, GCS and IPC were used for roughly the latter half of the study period. Dalteparin, an LMWH, was usually used for three days. Among 2,107 cases, only 1,268 (60%) were of malignant disease. The other 40% of patients underwent surgery for different forms of benign gynecological diseases. In contrast, only malignant cases were analyzed in our study. Moreover, not only PE, but also DVT, were included in the present study. Because radical surgery for malignant disease was clearly a high-risk factor for postoperative VTE, our data are possibly informative for evaluation of the time of susceptibility for postoperative VTE in gynecological malignant cases. Peedicayil *et al*. analyzed the incidence and timing of VTE after surgery for gynecological malignancies (16). In their study, 76% of VTE cases were diagnosed between eight and 90 days from the surgery for gynecologic cancer, although the maximum number of cases of VTE occurred in the first week. Precise data of the fraction of the patients who received prophylactic UFH or LMWH were not shown. Their monitoring procedure to detect suspicious PE after surgery was also not reported. In our study, all the patients received continuous SpO_2 monitoring until they finished their first walk on day 1, and measurement of circumference of the right and left thighs and legs before the first walk. All patients suspected for VTE underwent ultrasonography and chest MDCT screening for DVT and PE. These procedures might have resulted in the trend for earlier detection of VTE in our study, compared to theirs.

In light of the frequent occurrence of VTE long after surgery, as Peedicayil *et al*. have shown (16), it might be necessary to perform prophylaxis for longer periods. However, like our findings, postoperative VTEs were mostly detected soon after surgery, possibly as a result of our monitoring protocol, and the significance of extended use of VTE prophylactic procedures needs to be evaluated in

association with their costs. In the present study, we estimated the added costs for treatments with UFH, LMWH and fondaparinux until postoperative day 10, based on an estimation from previous studies (7, 18). In this analysis, a 9-day extended use of UFH, LMWH and fondaparinux was expected to be effective in preventing all VTEs which occurred during day 2 to day 10 in our study population. This analysis revealed that $617,783, $726,185, or $994,222 was necessary for continuous VTE prophylaxis of our entire cohort using UFH, LWMH or fondaparinux in order to prevent a mere eight VTEs in the 738 patients with malignant tumor in our study. These data suggested that additional prophylaxis until day 10 seems not to be very cost-effective; however, the distribution of races, incidence of VTE, charges for the procedures and insurance systems are different worldwide.

In our strategy, UFH, combined with GCS and IPS, was used only three times: 2 h preoperatively and 2 h and 14 h postoperatively; however, thorough SpO_2 monitoring and perioperative measurements of circumference of both sides of the thighs and calves were performed to detect VTE very soon after incidence. The administration of UFH resulted in no HIT occurrence in our study (data not shown). A larger and more prospective analysis is required to fully establish an appropriate strategy for prophylaxis of VTE in gynecological malignancies, and our results should provide a better framework for designing such a study.

Conclusion

A strategy which might be cost-effective for postsurgical management of gynecological malignances is perioperative use of UFH three times, with thorough SpO_2 monitoring, and perioperative measurement of the circumference of the right and left thighs and legs.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Details of Ethics Approval

All patients provided written informed consent before the treatments commenced. This study was approved by the Institutional Review Boards and Ethics Committees of the Osaka University Hospital.

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