Efficacy of Venous Thromboembolism Prophylaxis in Patients Undergoing Pelvic Cancer Surgery: A Randomized Controlled Trial

Piyanut Pootracool MD*, Kanoklada Srikuea MD*, Wiwat Tirapanich MD*,
Sopon Jirasiritum MD*, Surasak Leela-Udomlipi MD*, Suthas Horsirimanont MD*,
Nutsiri Kittitirapong MD*, Wisoot Kongchareonsombat MD**, Sarikapan Wilailak MD***

** Division of Vascular Surgery, Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*
*** Division of Urological Surgery, Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*
**** Department of Gynecologic Oncology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

Backgrounds: *Pelvic cancer surgery has a high risk for venous thromboembolism (VTE). Pharmacologic venous thromboprophylaxis is not routinely accepted among surgical practice in Thailand due to the awareness of major bleeding complication. However, ACCP guideline recommends mechanical prophylaxis to be initially used in this condition and pharmacologic prophylaxis is subsequently administered during postoperative period with minimal risk of bleeding. Therefore, it was possible to evaluate the efficacy of VTE prophylaxis in pelvic cancer surgery among our population.*
Objective: *To evaluate the efficacy and safety of VTE prophylaxis in pelvic cancer surgery.*
Material and Method: *Patients with pelvic cancer including gynecologic cancer and urologic cancer to undergo surgery were enrolled in the present study. The patients with colorectal cancer were excluded from the present study due to their declination. The present study randomized the patients into 2 groups regarding the receiving VTE prophylaxis. In prophylaxis group, intermittent pneumatic compression (IPC) was initially applied at intraoperative period and at least 3 days postoperatively until full ambulation. During the minimal risk of postoperative bleeding in this group, Enoxaparin (0.4 ml subcutaneous daily) was administered for 4 weeks. In control group, there was no VTE prophylaxis. Assessment of VTE was carried out at the 2nd and 5th week after surgery. Postoperatively, diagnosis of deep vein thrombosis (DVT) was performed by duplex ultrasonography and diagnosis of pulmonary embolism (PE) was initially done by clinical manifestations and then confirmed by computed tomographic angiography of pulmonary artery.*
Results: *A total of 108 pelvic cancer patients including 70 patients with gynecologic cancer and 38 patients with urologic cancer. The prevalence of proximal DVT after pelvic cancer surgery in the present study was 2.8%, which were 3.7% in control group and 1.8% in prophylaxis group (p = 1.000). The relative risk reduction was 50%. In gynecologic cancer patients, prevalence of postoperative proximal DVT was 6.5% in control group and 2.6% in prophylaxis group (p = 0.580). The relative risk reduction was 60%. There was no postoperative proximal DVT in urologic patients. Postoperative symptomatic PE was not found in this study. Bleeding complications was 3.7% (1.8% major bleeding and 1.8% minor bleeding) in prophylaxis group compared with 0% in control group (p = 0.495).*
Conclusion: *After the implementation of VTE prophylaxis in pelvic cancer surgery, the prevalence of postoperative proximal DVT was decreased with significant risk reduction in gynecologic cancer surgery and the risk of postoperative bleeding was acceptable. VTE prophylaxis program may be benefit in gynecologic cancer surgery in Thai population.*

Keywords: *Venous thromboembolism, cancer surgery, DVT prophylaxis, VTE prophylaxis, deep vein thrombosis, pulmonary embolism*

J Med Assoc Thai 2017; 100 (Suppl. 9): S220-S229
Full text. e-Journal: *http://www.jmatonline.com*

Correspondence to:
Pootracool P, Vascular and Transplant Unit, Department of Surgery, Ramathibodi hospital, Mahidol University, Bangkok 10400, Thailand.
Tel: 662-201-1527 # 233, Fax: 662-201-1316
E-mail: rappeg@gmail.com

Venous thromboembolism (VTE) is the most common fatal disease in western countries. The common risk factors are prolonged immobilization, trauma and post operation[1]. However, deep vein thrombosis (DVT) was an under-recognized disease in Thailand. In the epidemiologic study of Thai patients, the prevalence of this disease was 1: 1,000 of patients admitted in a university hospital. Malignancy was the predominant risk factors of proximal DVT with the prevalence of 39.9%. Genitourinary cancer (50.4%) was the most common malignancy found in the present study. Postoperative proximal DVT was found more commonly in cancer surgery than in non-cancer surgery (21.1% versus 11.9%, $p<0.028$)[2].

In general, cancer surgery has a 2-5 fold-increased risk for postoperative DVT[3]. Regarding pulmonary embolism (PE) as the fatal complication of DVT, pharmacologic venous thromboprophylaxis is routinely scheduled in cancer surgery. Unfortunately, this VTE prophylaxis was not routinely accepted during cancer surgery in Thailand due to the awareness of major bleeding complication. Currently, the American College of Chest Physicians (APCC) guideline recommends mechanical thromboprophylaxis to be initially used in surgery associated with high risk bleeding and pharmacologic thromboprophylaxis to be administered subsequently during postoperative period with minimal risk of bleeding. According to the safety of suggested international guideline, it was possible to evaluate the efficacy of VTE prophylaxis during pelvic cancer surgery in Thai patients by the first randomized controlled trial in Thailand.

Material and Method

Study design

The study was designed as a randomized controlled trial in a university hospital. This clinical study had the medical ethics committee approval of Ramathibodi Hospital, Mahidol University. The patients undergoing pelvic cancer surgery were randomized into two groups regarding the receiving of VTE prophylaxis; prophylaxis group and control group. The primary objective was to measure the risk reduction of postoperative VTE by the prophylaxis process. The secondary objectives included prevalence of postoperative proximal DVT and symptomatic PE in patients undergoing pelvic cancer surgery and bleeding complication in prophylaxis group.

Patient selection

All patients with the age above 18 years undergoing pelvic cancer surgery were included in this study. The process of enrollment was between April 2016 and January 2017. Patients with pelvic cancer were the ones who had the preoperative diagnosis of gynecologic cancer and urologic cancer. Patients with colorectal cancer were not included in the present study due to their declination. Pelvic cancer surgery with operative duration less than 45 minutes was also excluded from the present study. The patient exclusion criteria included preoperative VTE within 3 months, current use of anticoagulant or antiplatelet or thrombolytic agent, pregnancy, immobilization more than 3 days, peripheral arterial occlusive disease with ankle-brachial index less than 0.8, renal dysfunction with glomerular infiltration rate below 30 mL/min/1.73 sqm, congestive heart failure with leg swelling, skin infections, contraindication to anticoagulation, recent active bleeding, previous history of heparin-induced thrombocytopenia or hypersensitivity of low molecular weight heparin, platelet count less than 70,000 cells/cu.mm, activated partial thromboplastin time or prothrombin time over 1.5 times of control value.

After informed consent, all patients had preoperative VTE screening by clinical assessment of DVT and PE, and duplex ultrasonography on both legs. The suitable patients were randomized into 2 groups regarding the use of VTE prophylaxis. The process of grouping was 1:1 ratio by block 4 randomization.

Interventions

In prophylaxis group, intermittent pneumatic compression (IPC) was used as mechanical VTE prophylaxis during intraoperative period and post operation until the day of normal ambulation. The intermittent pneumatic device (IPD, Kendall SCD™ express sequential compression system) was applied on bilateral lower extremities for 18 hours per day. Postoperatively without bleeding risk, Enoxaparin (Clexane, Sanofi KK) subcutaneous injection 0.4 ml once daily was commenced and continued for 4 weeks after surgery. In control group, there was no VTE prophylaxis regimen.

Assessment outcomes

Postoperatively, VTE was classified into proximal DVT And symptomatic PE. Diagnosis of proximal DVT was performed by the color duplex ultrasound with 5 to 10 MHz lineal transducers at the 2nd and the 5th week after surgery. The criteria of diagnosis included venous compression test, flow augmentation during calf compression, color Doppler

filling in the veins and respiratory phase variation in iliac veins, common femoral veins, femoral veins and popliteal veins. Diagnosis of PE was done initially by clinical manifestation including dyspnea, chest pain, hemoptysis and oxygen desaturation. CTA pulmonary artery was the final investigation for PE diagnosis.

Criteria of major bleeding included one of the followings; fatal bleeding, requirement of 2 units of blood transfusion, decreased hemoglobin level of 2 g/dL, evidence of bleeding in retroperitoneal space, intracranial region and intraocular area, bleeding with subsequent myocardial infarction or stroke, bleeding required surgical of interventional control. Bleeding without those crirteria was considered to be minor.

The information of patients in both groups on demographic data, comorbidities, characteristic of diseases, types of operation, evidence of postoperative VTE, and bleeding complication were recorded and analyzed.

Sample size and statistical methods

The sample size was calculated with two independent proportion (two-tailed test). Previous study determined that relative risk estimated of intermittent pneumatic compression prophylaxis in medical and surgical patients were 0.48[14]. This method reduced the risk of symptomatic VTE about >50%[9]. The study required a sample size of 54 patients each group to achieve a precision of 95% confidence interval. Statistical analyses were conducted by using Stata 14 software. Student's t-tests were used for mean comparisons, and χ^2-tests for proportion comparisons. Fisher's exact tests were used to examine statistical significance for proportion comparisons if any of the compared counts were less than 5. A p-value <0.05 was considered to be statistically significant. Power of 80% also was considered.

Results

Demographics data

A total of 118 patients were requested to enroll in this study and 108 of them were randomized to receive either with or without VTE prophylaxis. Among the ten patients excluded from randomization, they were one patient with prolonged immobilization, two patients with previous DVT within 3 months, two patients with renal dysfunction (GFR <30 mL/min/1.73 m^2), three patients currently on antiplatelet, and two patients declining for participation (Fig. 2).

Among 108 randomized patients, they were 54 patients in prophylaxis group and 54 patients in control group. There was no statistical difference in the majority of demographic information between the two groups except for varicose vein (22.2% versus 7.4%, p = 0.030) and oral hormonal contraception (16.7% versus 5.6%, p = 0.002) significantly higher in prophylaxis group (Table1).

The disease characteristics were demonstrated. There was no statistically significant difference in patient demographics between the two groups. Most patient undergone gynecologic surgery (72.2% in prophylaxis and 57.4% in control groups). Almost diagnosis or suspected primary cancer was prostate cancer about thirty-two percent of patients. However, seven patients had benign pathologic result that consist of six patients of suspected ovarian cancer

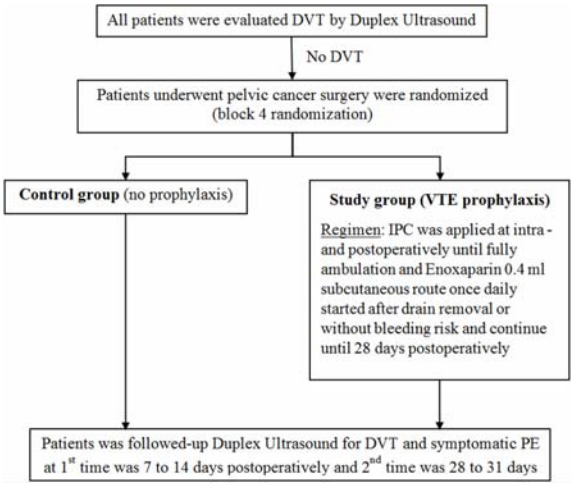

Fig. 1 Study protocol (DVT = deep vein thrombosis, PE = pulmonary embolism, IPC = intermittent pneumatic compression, VTE = venous thrombo-embolism)

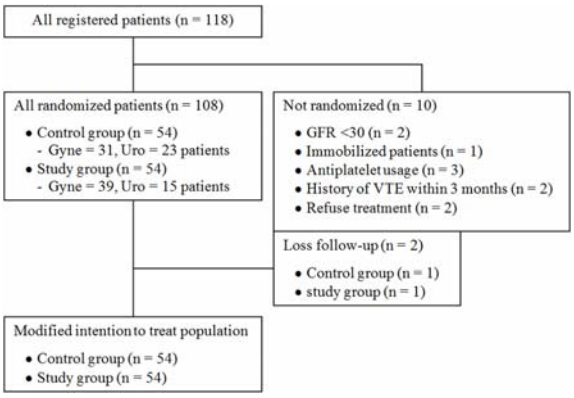

Fig. 2 Disposition of patients were randomly assigned to or control group (without prophylaxis).

and a one patient of suspected endometrial cancer at preoperative period. Our study used intention to treat for data analysis. Only eight patients had metastatic disease (Table 2).

Regarding the characteristic of diseases (Table 2), there was no statistical difference in the ratio of gynecologic disease and urologic disease between the two groups (prophylaxis group 72.2%: 27.8% and control group 57.4%: 42.6%). However, the number of ovarian cancer was higher in prophylaxis group than control group (35.2% versus 18.5%, $p = 0.157$). The number of benign disease was more in control group compared with prophylaxis group (11.1% versus 1.9%). They were no difference in disease staging and tumor size between the two groups.

Surgical procedure and related events also were no statistically significant difference in patient demographics between the two groups. Most patients underwent laparotomy surgery (70.4% in prophylaxis and 61.1% in control groups) that combined pelvic

Table 1. Baseline demographics and characteristics of the modified intention to treat population who underwent pelvic cancer surgery (BMI = body mass index, VTE = venous thromboembolism, COPD = chronic obstructive pulmonary disease)

Characteristics	Study group (n = 54)	Control group (n = 54)	*p*-value
Female, n (%)	39 (72.2)	32 (59.2)	0.156
Age (year), mean (SD)	60.0 (10.5)	60.9 (12.7)	0.680
BMI (kg/ml^2), mean (SD)	27.4 (9.5)	24.9 (4.7)	0.086
COPD, n (%)	3 (5.6)	0 (0)	0.243
Oral contraception, n (%)	12 (22.2)	4 (7.4)	0.030
Hormonal therapy, n (%)	2 (3.7)	1 (1.9)	1.000
Previous cancer, n (%)	4 (7.4)	3 (5.6)	1.000
Varicose vein, n (%)	15 (16.7)	3 (5.6)	0.002
Central venous catheter, n (%)	0 (0)	1 (1.9)	1.000
Caprini score, n (%)			0.057
Low to moderate VTE risk (score 2 to 4)	0 (0)	4 (7)	
High VTE risk (score ≥5)	54 (100)	50 (93)	

Table 2. Disease characteristics (*Seven patients had benign pathologic result that consist of six patients of suspected ovarian cancer and a one patient of suspected endometrial cancer at preoperative period, VTE = venous thromboembolism)

Characteristics	VTE prophylaxis (n = 54)	Control (n = 54)	*p*-value
Therapeutic area, n (%)			0.107
Gynecologic surgery	39 (72.2)	31 (57.4)	
Urologic surgery	15 (27.8)	23 (42.6)	
Primary cancer, n (%)			0.157
Endometrial cancer	14 (25.9)	16 (29.6)	
Ovarian cancer	19 (35.2)	10 (18.5)	
Cervical cancer	6 (11.1)	5 (9.3)	
Prostate cancer	15 (27.8)	20 (37.0)	
Bladder cancer	0 (0)	3 (5.6)	
Staging, n (%)			0.344
I	20 (37.0)	18 (33.3)	
II	13 (24.0)	10 (18.5)	
III	15 (27.8)	17 (31.5)	
IV	5 (9.3)	3 (5.6)	
Benign*	1 (1.9)	6 (11.1)	
Tumor size, median (min, max)	2 (1,25.7)	3.65 (1, 30)	0.130

lymph node dissection (81.5% and 68.5%, respectively). In subgroup analysis, ninety-four percent of gynecologic surgery underwent to laparotomy and fifty-seven percent and twenty-nine percent of urologic surgery performed robotic surgery and laparoscopic surgery, respectively. All patients required general anesthesia. In prophylaxis group, 14.9% of patients had residual tumor after operation and more than control group. This result was statistic significant (Table 3).

According to the information of surgical procedures (Table 3), there were no statistical difference in types of operation, operative time, and types of anesthesia between the two groups. In gynecologic cancer, most patients (94%) underwent laparotomy surgery combining with pelvic lymph node dissection. On the contrary, the robotic surgery (57%) and the laparoscopic surgery (29%) were the common types of treatment in urologic cancer. However, the evidence of residual tumor was higher in prophylaxis group than in control group (14.9% versus 3.7%, $p = 0.046$) (Table 3).

Prophylaxis regimen was used in 54 patients. The mean duration of IPC usage was 2.1±0.6 days. The medium duration of anticoagulant was 18 day (minimum duration was 5 day and maximum was 26 days). Two patients developed bleeding event after enoxaparin administration. One patient had vaginal stump bleeding and infection at Day 17 after enoxaparin administration. The patients underwent reoperation for vaginal stump repair and enoxaparin was discontinued. Another patient developed wound hematoma at Day 5 after enoxaparin administration, so the management was open wound and wound dressing also enoxaparin was discontinued (Table 4).

Regarding the information of VTE prophylaxis regimens (Table 4), the mean duration of IPC usage was 2.1±0.6 days. There was no complication of IPC. The medium duration of low molecular weight heparin (LMWH) injection was 18 days (range 5 to 26 days). Bleeding complication occurred in two patients. The first one had vaginal stump bleeding at day 17 of enoxaparin injection. This major bleeding was treated

Table 3. Surgical procedure and related events (VTE = venous thromboembolism)

Data	VTE prophylaxis (n = 54)	Control (n = 54)	*p*-value
Type of operation, n (%)			0.564
Laparotomy surgery	38 (70.4)	33 (61.1)	
Laparoscopic surgery	7 (13.0)	8 (14.8)	
Robotic surgery	6 (16.6)	13 (24.1)	
Operative time, min(median)	180 (65,420)	155 (50,600)	0.420
General anesthesia, n (%)	54 (100)	54 (100)	1.000
Residual tumor, n (%)	8 (14.9)	2 (3.7)	0.046
Position			0.161
Supine, n (%)	38 (70.4)	31 (57.4)	
Lithotomy, n (%)	16 (29.6)	23 (42.6)	
Pelvic lymph node dissection, n (%)	44 (81.5)	37 (68.5)	0.120

Table 4. Prophylaxis regimen data (VTE = venous thromboembolism, IPC = intermittent pneumatic compression), * Vaginal stump bleeding, + Wound hematoma

Characteristics	VTE prophylaxis (n = 54)	Control (n = 54)
Hospital stay, min (median)	4 (3, 22)	4 (3, 20)
Loss follow-up, n (%)	1 (1.9)	1 (1.9)
Duration of IPC usage (days), mean (SD)	2.1 (0.6)	0 (0)
Complication of IPC	0 (0)	0 (0)
Duration of anticoagulant, days (median)	18 (5, 26)	0 (0)
Bleeding events, n (%)	2 (3.8)	
Minor bleeding*	1 (1.9)	0 (0)
Major bleeding+	1 (1.9)	0 (0)

by surgical repair and discontinuation of LMWH. The second patient had hematoma of surgical wound at day5 of enoxaparin injection without expansion and blood transfusion. This minor bleeding was treated by blood clot removal.

Characteristic of patients with acute proximal deep vein thrombosis

Three patients who underwent gynecologic surgery developed DVT. The urological surgery had none of the DVT events. None of the patients developed PE. Among two cases of postoperative proximal DVT in the control group, one case was diagnosed with ovarian cancer and had left femoropopliteal DVT. Another one case had endometrial cancer and developed right popliteal DVT. Although VTE prophylaxis regimen was applied, one patient developed left femoropopliteal DVT. The patient had Infected midline wound hematoma at Day 8 postoperatively, so the gynecologist discontinued enoxaparin and the patient received hematoma evacuation and wound dressing. Two weeks after discontinuation of enoxaparin, the patient developed left thigh and calf swelling. Duplex ultrasound showed evidence of DVT.

In the present study, 3 patients had postoperative proximal DVT with the prevalence of 2.7: 100. All of them were gynecologic cancer patients with 2 of endometrial cancer and 1 of ovarian cancer. The sites of proximal DVT were common femoral vein in 2 and popliteal vein in 1. The Caprini score was between 6 and 7 among these patients (Table 5).

Incidence and efficacy

The overall incidence of VTE and DVT in pelvic cancer surgery in the prophylaxis group was less than the control group. The incidence of DVT was 1.9% (1/54 patients) in prophylaxis group and 3.7% (2/54 patients) in control group. Relative risk was 0.5 (95% CI 0.05 to 5.35) and relative risk reduction was 50%. The number needed to treat was 53. In subgroup analysis, the incidence of DVT was 2.6% in prophylaxis group and 6.5% in control group but the results were not statistically significant (Table 6).

Postoperative proximal DVT in the present study was lower in prophylaxis group compared with control group (1.8% versus 3.7%). The relative risk was 0.5 (95% CI 0.05 to 5.35) and the relative risk reduction was 50%. The number needed to treat was 53. In gynecologic cancer patients, postoperative proximal DVT was less in prophylaxis group than in control group (2.6% and 6.5%). The relative risk was 0.4 (95% CI 0.04 to 4.18) and the relative risk reduction was 60%. The number needed to treat was 108. There were no

Table 5. Characteristic case of postoperative acute asymptomatic proximal DVT (DVT = deep vein thrombosis, Dx = diagnosis, Serous CA = serous carcinoma, Adeno CA = adenocarcinoma, CFV = common femoral vein, Pop v = popliteal vein, Lt. = left, Rt. = right)

Case	Age (years)	Caprini score	Time of DX (post-op)	Organ	Type of cancer	Staging	Site of DVT
1	64	6	Day 13	Ovary	Serous CA	II	Lt. CFV + Pop V
2	62	7	Day 10	Endometrium	Dedifferentiate	I	Rt. Pop v
3*	53	7	Day 22	Endometrium	Adeno CA	I	Lt. CFV + Pop V

* Patient was randomized to prophylaxis group

Table 6. Incidence of venous thromboembolism events (VTE = venous thromboembolism, PE = pulmonary embolism, DVT = deep venous thrombosis, CI = confidence interval)

Events	VTE prophylaxis, n (%)	Control, n (%)	Relative risk (95% CI)	*p*-value
VTE	1.9 (1/54)	3.7 (2/54)	0.5 (0.05 to 5.35)	1.000
Symptomatic PE	0 (0/54)	0 (0/54)		
DVT in pelvic cancer patients	1.9 (1/54)	3.7 (2/54)	0.5 (0.05 to 5.35)	1.000
DVT in gynecologic patients	2.6 (1/39)	6.5 (2/31)	0.4 (0.04 to 4.18)	0.580
DVT in urologic patients	0 (0/15)	0 (0/23)		

postoperative proximal DVT in urologic cancer patients and no postoperative symptomatic PE in the present study.

Discussion

The present study was the first randomized controlled trial for VTE prophylaxis in pelvic cancer surgery in Thailand.

VTE was considered to be an important cause of death in hospitalized patients, especially in those underwent major surgery. Routine VTE prophylaxis in western medical center has increasing data. Generally, most physicians do not recognize the implementation of VTE prophylaxis in the practice among Asian populations. Some reports showed varied results of the incidence of postoperative DVT in general and colorectal surgery[7]. However, other reports exhibited that postoperative DVT was rare[15,16]. In addition, almost every physicians concern more about postoperative bleeding complications. No previous randomized research was performed to identify incidence of VTE in pelvic cancer surgery in Asia and the efficacy of VTE prophylaxis implement following the ACCP guideline for patients who had high risk for major bleeding complications.

The present study, the author randomized patients who underwent pelvic cancer surgery and observed the incidence of postoperative acute asymptomatic proximal DVT and PE. The results show that the incidence of proximal DVT in pelvic cancer surgery was low according to previous Asian research[17-19]. DVT in prophylaxis group was 1.9% which lower than the control group (3.7%). In prophylaxis group, the patient developed DVT on postoperative day 22 because of stopped anticoagulant from hematoma at surgical wound. Nonetheless, the result was not statistically significant between the two groups. Patients who developed DVT underwent gynecologic cancer surgery only, it was not found in urological cancer surgery. Some research demonstrated the higher rate of incidence of venous thrombosis in gynecologic cancer than in urological cancer[20]. Type of surgical technique may be predisposing factor for developed DVT such as open surgical technique causing traction, compression, manipulation structure in pelvic cavity and pelvic vein but laparoscopic and robotic surgery less invasive. Most of urological cancer cases underwent robotic or laparoscopic surgery and some study reported decreasing incidence of DVT and/or PE following robot-assisted surgeries[21]. Interestingly results from gynecologic subgroup analysis, incidence of proximal DVT was 2.6% and 6.5% in prophylaxis and control group, respectively. According to recent VTE guideline, the gynecological cancer surgery patients were classified as high risk for VTE development. The incidence of DVT in the absence of pharmacologic and mechanical prophylaxis was 6% or more[2]. The author implied that gynecologic cancer in Thai patients was high risk operation for VTE.

From the present study protocol, VTE prophylaxis could reduce the risk of proximal DVT about 50%. These results were similar to research in Japanese patients who underwent pelvic cancer surgery[13], however difference of prophylaxis protocol between study were drug dosing, time to initiate usage and duration of pharmacological prophylaxis. In present study, there were no case of fatal bleeding and only 2 cases of 54 cases had bleeding events, therefore bleeding risk was acceptable after enoxaparin usage.

The low incidence of postoperative proximal DVT in present study can be explained. First, most of the cases were not advanced stage of cancer and most of the cases were curative resection. Second, the patient status were enrolled good mobilization and fit for surgery. Third, patients were ambulated early postoperative period day 1 to 2. Fourth, genetic different was considered because some study demonstrated Asian population had low prevalence of factor V leiden mutation and prothrombin G20210A[6,22]. So, incidence of VTE was lower in Asian than Western population. Furthermore, the present study detected only asymptomatic proximal DVT, not included calf DVT. Fifth, the patient in prophylaxis group more advanced stage of cancer and residual tumor than control group result in the incidence of DVT in prophylaxis group was low.

The limitation of this study were small sample size and duplex ultrasound could detect only distal iliac vein DVT. Visualization of at least one iliac vein segment has been reported in up to 79% of ultrasound studies, the common iliac vein was adequately imaged in only 47%[23].

Nevertheless, the author appreciated Thai patients underwent pelvic cancer surgery with high risk for major bleeding complication could applied VTE prophylaxis implement following the ACCP guideline. Because it tends to decrease the incidence of VTE if VTE prophylaxis was used.

Conclusion

The incidence of VTE tends to decrease after the implementation of recommended prophylaxis. And

the risk of postoperative bleeding is low and acceptable, so VTE prophylaxis may be benefit in Thai patients undergo pelvic cancer surgery with acceptable risk for bleeding complication. The further large study may be need to demonstrate of significant reduction benefit in VTE prophylaxis.

What is already known on this topic?

Venous thromboembolism (VTE) is recommended in patients undergoing pelvic cancer surgery. Multiple randomized controlled trials (RCTs) have show the efficacy of thromboprophylaxis in reducing the incidence of VTE.

What this study adds?

VTE prophylaxis in pelvic cancer surgery in Thai patients are not routine practice because cancer risk of bleeding. The findings support that VTE prophylaxis can decrease the incidence of VTE in patients undergoing pelvic cancer surgery with acceptable bleeding risk.

Acknowledgements

The authors acknowledge Ms. Nipapan Choonu for assistance in the study.

Potential conflicts of interest

None.

References

1. Lyman GH, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, Balaban EP, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013; 31: 2189-204.
2. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141 (2 Suppl): e227S-77S.
3. Samama CM, Boubli L, Coloby P, Debourdeau P, Gruel Y, Mariette C, et al. Venous thromboembolism prophylaxis in patients undergoing abdominal or pelvic surgery for cancer—a real-world, prospective, observational French study: PReOBS. Thromb Res 2014; 133: 985-92.
4. Warwick D, Samama MM. The contrast between venographic and clinical endpoints in trials of thromboprophylaxis in hip replacement. J Bone Joint Surg Br 2000; 82: 480-2.
5. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133 (6 Suppl): 381S-453S.
6. Zakai NA, McClure LA. Racial differences in venous thromboembolism. J Thromb Haemost 2011; 9: 1877-82.
7. Liew NC, Moissinac K, Gul Y. Postoperative venous thromboembolism in Asia: a critical appraisal of its incidence. Asian J Surg 2003; 26: 154-8.
8. Sermsathanasawadi N, Thangrod R, Hongku K, Wongwanit C, Ruangsetakit C, Chinsakchai K, et al. Prevalence of perioperative asymptomatic proximal deep vein thrombosis in Thai gynecologic cancer patients. J Med Assoc Thai 2014; 97: 153-8.
9. Sadaghianloo N, Dardik A. The efficacy of intermittent pneumatic compression in the prevention of lower extremity deep venous thrombosis. J Vasc Surg Venous Lymphat Disord 2016; 4: 248-56.
10. Laporte S, Liotier J, Bertoletti L, Kleber FX, Pineo GF, Chapelle C, et al. Individual patient data meta-analysis of enoxaparin vs. unfractionated heparin for venous thromboembolism prevention in medical patients. J Thromb Haemost 2011; 9: 464-72.
11. Nagata C, Tanabe H, Takakura S, Narui C, Saito M, Yanaihara N, et al. Randomized controlled trial of enoxaparin versus intermittent pneumatic compression for venous thromboembolism prevention in Japanese surgical patients with gynecologic malignancy. J Obstet Gynaecol Res 2015; 41: 1440-8.
12. Lensing AW, Prandoni P, Brandjes D, Huisman PM, Vigo M, Tomasella G, et al. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. N Engl J Med 1989; 320: 342-5.
13. Sakon M, Kobayashi T, Shimazui T. Efficacy and safety of enoxaparin in Japanese patients undergoing curative abdominal or pelvic cancer surgery: results from a multicenter, randomized, open-label study. Thromb Res 2010; 125: e65-70.
14. Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, et al. Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis. Health Technol Assess

2005; 9: iii-iv, ix-x, 1-78.
15. Jakhetiya A, Shukla NK, Deo SV, Garg PK, Thulkar S. Deep Vein Thrombosis in Indian Cancer Patients Undergoing Major Thoracic and Abdomino-Pelvic Surgery. Indian J Surg Oncol 2016; 7: 425-9.
16. Nelson DW, Simianu VV, Bastawrous AL, Billingham RP, Fichera A, Florence MG, et al. Thromboembolic Complications and Prophylaxis Patterns in Colorectal Surgery. JAMA Surg 2015; 150: 712-20.
17. Sakon M, Maehara Y, Yoshikawa H, Akaza H. Incidence of venous thromboembolism following major abdominal surgery: a multi-center, prospective epidemiological study in Japan. J Thromb Haemost 2006; 4: 581-6.
18. Chan SY, Leung VF, Yee CH, Chan ES, Hou SS, Chu W, et al. Incidence of postoperative deep vein thrombosis after robotic-assisted laparoscopic prostatectomy: a prospective study in Chinese patients. Int Urol Nephrol 2014; 46: 2139-42.
19. Kanchanabat B, Stapanavatr W, Manusirivithaya S, Srimantayamas S. The rate and mortality of postoperative venous thromboembolism of moderate risk surgery in Asian patients without thrombo-prophylaxis: systematic review with meta-analysis. World J Surg 2014; 38: 194-202.
20. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. Blood 2013; 122: 1712-23.
21. Secin FP, Jiborn T, Bjartell AS, Fournier G, Salomon L, Abbou CC, et al. Multi-institutional study of symptomatic deep venous thrombosis and pulmonary embolism in prostate cancer patients undergoing laparoscopic or robot-assisted laparoscopic radical prostatectomy. Eur Urol 2008; 53: 134-45.
22. Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. N Engl J Med 2001; 344: 1222-31.
23. Messina LM, Sarpa MS, Smith MA, Greenfield LJ. Clinical significance of routine imaging of iliac and calf veins by color flow duplex scanning in patients suspected of having acute lower extremity deep venous thrombosis. Surgery 1993; 114: 921-7.

ประสิทธิภาพของการป้องกันการเกิดภาวะลิ่มเลือดอุดตันในหลอดเลือดดำในผู้ป่วยไทยที่ได้รับการรับการผ่าตัดมะเร็งในอุ้งเชิงกราน: การศึกษาแบบสุ่มมีกลุ่มควบคุม

ปิยนุช พูตระกูล, กนกลดา ศรีเกื้อ, วิวัฒน์ ลิระพานิช, โสภณ จิรสิริธรรม, สุรศักดิ์ ลีลาอุดมลิปี, สุทัศน์ ฮ้อศิริมานนท์, ณัฐสิริ กิตติลิระพงษ์, วิสูตร คงเจริญสมบัติ, สฤกพรรณ วิไลลักษณ์

ภูมิหลัง: การผ่าตัดมะเร็งในอุ้งเชิงกรานมีปัจจัยเสี่ยงสูงต่อการเกิดภาวะลิ่มเลือดอุดตันในหลอดเลือดดำ การให้ยาป้องกันการเกิดภาวะดังกล่าวยังไม่เป็นที่ยอมรับในเวชปฏิบัติทางด้านศัลยกรรม เนื่องจากมีความกังวลเกี่ยวกับภาวะแทรกซ้อนที่จะตามมาคือเลือดออก แต่อย่างไรก็ตามแนวทางการให้การป้องกันภาวะลิ่มเลือดอุดตันในหลอดเลือดดำสามารถใช้เครื่องบีบรัดน่องได้ในระยะเริ่มแรก หลังผ่าตัดและตามด้วยการให้ยาป้องกันภาวะดังกล่าวในเวลาต่อมา ซึ่งตามแนวทางการปฏิบัตินี้จะมีปัจจัยเสี่ยงน้อยต่อการเกิดภาวะเลือดออก ดังนั้นจึงได้ศึกษาถึงประสิทธิภาพของแนวทางการป้องกันการเกิดภาวะลิ่มเลือดอุดตันในหลอดเลือดดำในการผ่าตัดมะเร็งในอุ้งเชิงกราน

วัตถุประสงค์: มะเร็งในอุ้งเชิงกรานมีปัจจัยเสี่ยงสูงต่อการเกิดลิ่มเลือดอุดตันในหลอดเลือดดำและเกิดภาวะแทรกซ้อนเรื่องเลือดออกมาก สำหรับแนวทางการป้องกันภาวะลิ่มเลือดอุดตันในหลอดเลือดดำไม่ได้ใช้กันแพร่หลายในเวชปฏิบัติ แต่อย่างไรก็ตามแนวทางการป้องกันการเกิดลิ่มเลือดอุดตันในหลอดเลือดดำตามแนวทางป้องกันของ ACCP แนะนำให้ใช้การป้องกันโดยวิธีใส่ถุงน่องหรือเครื่องบีบรัดน่องเป็นระยะ ๆ จนกว่าปัจจัยเสี่ยงเรื่องเลือดจะหมดไป ในการศึกษาได้ประเมินประสิทธิภาพของการป้องกันภาวะลิ่มเลือดอุดตันในการผ่าตัดมะเร็งอุ้งเชิงกราน

วัสดุและวิธีการ: ผู้ป่วยมะเร็งทั้งหมด 108 ราย มะเร็งทางนรีเวช 70 ราย มะเร็งทางศัลยกรรมระบบทางเดินปัสสาวะ 38 ราย ในการศึกษานี้เป็นการศึกษาแบบสุ่มและมีกลุ่มควบคุมโดยมีการใช้เครื่องบีบรัดน่องเป็นระยะ ๆ อย่างน้อย 3 วัน จนกว่าผู้ป่วยจะเริ่มเดินได้และให้ยา Enoxaparin 0.4 ซีซี ฉีดใต้ผิวหนังวันละครั้ง โดยเริ่มให้ยาฉีดหลังจากนำสายระบายน้ำเหลืองออกหรือหลังจากผู้ป่วยกลับบ้านจนกระทั่ง 4 สัปดาห์หลังผ่าตัดการวินิจฉัยภาวะหลอดเลือดดำอุดตันสามารถวินิจฉัยได้โดยตรวจอัลตราซาวด์หลอดเลือดและวินิจฉัยภาวะลิ่มเลือดอุดตันที่ปอดจากอาการแสดง ซึ่งจะได้รับการตรวจติดตามผลดังกล่าวในวันที่ 7 ถึง 14 และวันที่ 28 ถึง 31 หลังผ่าตัด ผลการศึกษาต้องการศึกษาถึงอัตราการลดลงของความเสี่ยงในภาวะหลอดเลือดดำอุดตันชนิดไม่มีอาการในขณะที่ได้รับการป้องกันการเกิดภาวะลิ่มเลือดอุดตัน

ผลการศึกษา: อุบัติการณ์การเกิดหลอดเลือดดำอุดตันชนิดไม่มีอาการมีร้อยละ 2.8 (ผู้ป่วยมะเร็งนรีเวช 3 ราย) ร้อยละ 3.7 ในกลุ่มควบคุม และร้อยละ 1.9 ในกลุ่มป้องกันหลังการผ่าตัด ($p = 1.000$) อัตราการลดลงของความเสี่ยงเป็นร้อยละ 50 ในการศึกษาวิเคราะห์กลุ่มย่อยของมะเร็งนรีเวชพบว่าอุบัติการณ์การเกิดภาวะหลอดเลือดดำอุดตันเป็นร้อยละ 6.5 ในกลุ่มควบคุมและร้อยละ 2.6 ในกลุ่มป้องกัน ($p = 0.580$) อัตราการลดลงของความเสี่ยงสัมพันธ์ (relative risk reduction) เป็นร้อยละ 60 ในการศึกษานี้ไม่พบอาการแสดงลิ่มเลือดอุดตันที่ปอดแต่มีภาวะแทรกซ้อนของการมีเลือดออกในผู้ป่วย 2 ราย โดยเกิดจากแผลมีเลือดคั่งและเลือดออกที่ตำแหน่งของแผลส่วนต้นของช่องคลอดที่เกิดจากการตัดมดลูก

สรุป: อุบัติการณ์การเกิดภาวะลิ่มเลือดอุดตันภายหลังการผ่าตัดจะลดลงได้ถ้ามีการปฏิบัติตามแนวทางของการให้การป้องกันภาวะดังกล่าวและภาวะแทรกซ้อนเรื่องเลือดออกมีอุบัติการณ์ต่ำเป็นที่ยอมรับได้ ดังนั้นการพิจารณาให้การป้องกันภาวะลิ่มเลือดอุดตันในหลอดเลือดดำอาจจะได้ประโยชน์ในการผ่าตัดมะเร็งในอุ้งเชิงกราน