Original Article

Outcomes Comparison between Low Molecular-Weight Heparin with Mechanical Prophylaxis versus Mechanical Prophylaxis Alone for Perioperative Venous Thromboembolism Prevention in Abdominopelvic Surgery: A Randomized Controlled Trial

Nutsiri Kittitirapong, MD[1], Parach Sirisriro, MD[1], Wiwat Tirapanich, MD[1], Sopon Jirasiritum, MD[1], Surasak Leela-Udomlipi, MD[1], Suthas Horsirimanont, MD[1], Chumpon Wilasrsamee, MD[2], Chairat Supsamutchai, MD[2], Pitichote Hiranyatheb, MD[2], Samart Phuwapraisirisan, MD[2], Jakrapun Jirasiritum, MD[2], Preeda Sumritpradit, MD[3], Tharin Thampongsa, MD[3], Pongsasit Singhatas, MD[3], Piyanut Pootracool, MD[1]

[1] Division of Vascular Surgery, Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[2] Division of General Surgery, Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[3] Division of Trauma and Surgical Critical Care, Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Background: Pharmaco-mechanical prophylaxis has been recommended for venous thromboembolism (VTE) prevention in surgical patients. The rate of receiving pharmacological prophylaxis was low due to the bleeding concern. The mechanical prophylaxis; either intermittent pneumatic compression (IPC) or graduated compressive stocking (GCS), becomes a preferred method, although its VTE incidence was higher than pharmaco-mechanical prophylaxis. The combination of IPC and GCS had a lower risk of DVT than GCS alone. We examined the efficacy of combining mechanical prophylactic methods; IPC and GCS, in VTE prophylaxis.

Objective: The present study aimed to compare the pharmaco-mechanical method with combining mechanical method in VTE prophylactic effectiveness and adverse events for elective abdominopelvic surgery.

Materials and Methods: A randomized controlled trial was conducted in elective abdominopelvic surgical patients. The control group received low molecular weight heparin, IPC, and GCS, whereas the study group received IPC and GCS.

Results: We enrolled 76 elective abdominopelvic surgical patients, 39 patients in the control group, and 37 patients in the study group. Surgery for cancer was accounted for 64 (84.2%) and Caprini score was 8.4 (±1.95). The incidence of perioperative VTE was 5 (6.58%). All VTE cases were asymptomatic DVT. In the present study group, 1 (2.7%) of proximal DVT and 3 (8.1%) of calf vein DVT occurred. Only 1 (2.6%) of proximal DVT occurred in the control group. The incidence of VTE tended to be higher in the present study group than in the control group; 4 (10.8%) vs. 1 (2.6%); RR 4.22, 95% CI 0.49 to 36.00, p-value=0.194). The adverse event such as symptomatic pulmonary embolism (PE), bleeding complication, and readmission rate was not found.

Conclusion: The effectiveness of IPC combined with GCS was not superior to pharmaco-mechanical thromboprophylaxis for VTE prevention in high-risk surgical patients.

Keywords: VTE cancer surgery, DVT prophylaxis, VTE prophylaxis, DVT, PE, Deep vein thrombosis, Pulmonary embolism, mechanical thromboprophylaxis, Intermittent pneumatic compression (IPC), Graduated compression stockings (GCS)

J Med Assoc Thai 2021;104(Suppl.5): S1-9
Website: http://www.jmatonline.com

Correspondence to:

Kittitirapong N.

Division of Vascular Surgery, Department of Surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand

Phone: +66-2-2011316, **Mobile:** +66-85-5539293

Email: nutsiri.kit@mahidol.ac.th

How to cite this article:

Kittitirapong N, Sirisriro P, Tirapanich W, Jirasiritum S, Leela-Udomlipi S, Horsirimanont S, Wilasrsamee C, Supsamutchai C, Hiranyatheb P, Phuwapraisirisan S, Jirasiritum J, Sumritpradit P, Thampongsa T, Singhatas P, Pootracool P. Outcomes Comparison between Low Molecular-Weight Heparin with Mechanical Prophylaxis versus Mechanical Prophylaxis Alone for Perioperative Venous Thromboembolism Prevention in Abdominopelvic Surgery: A Randomized Controlled Trial. J Med Assoc Thai 2021;104 (Suppl.5): S1-9.

doi.org/10.35755/jmedassocthai.2021.S05.00061

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), has become increasingly recognized as a significant public health burden, especially hospital-acquired VTE in patients undergoing major surgery. The risk of VTE is estimated to be 20% for general surgical patients and cancer surgery also has a 2 to 5 folds increased risk for postoperative VTE[1]. Thromboprophylaxis is the most important management for surgical safety strategy.

Thromboprophylaxis consists of pharmacologic and mechanical measures to diminish the risk of DVT and PE. The decision to initiate thromboprophylaxis should be based on the patient's risk of thromboembolism and bleeding[1].

The incidence of symptomatic VTE in patients who received pharmaco-mechanical prophylaxis was less than in mechanical prophylaxis alone[1,2]. When pharmacological thromboprophylaxis was contraindicated, mechanical prophylaxis might be a reasonable option. However, this monotherapy has not been sufficiently prevented VTE. Turpie, et al[3] found the VTE rate was significantly lower in the LMWH combined with intermittent pneumatic compression (IPC) than IPC alone, but there was significantly higher major bleeding in the LMWH arm as well.

According to ACCP 2008[2] and ACCP 2012[1] Guideline, mechanical prophylaxis was divided into two methods: graduated compressive stocking (GCS) and IPC. These guidelines recommended using IPC was preferable to GCS. There was no recommendation for combining mechanical methods using IPC with GCS. For mechanical prophylaxis, the results of the meta-analysis showed GCS alone and IPC alone reduced the risk of DVT by 65%[4] and 66%[5,6], respectively. The combination of IPC and GCS in gynecological surgery had a lower risk of DVT than GCS alone by 62%[7]. We hypothesis whether combining mechanical methods could prevent VTE and lowering bleeding risk in high-risk bleeding surgical patients. These led us to hypothesis the effectiveness of combining mechanical prophylaxis comparing with pharmaco-mechanical prophylaxis in the patients undergoing abdominopelvic surgery with a high risk of bleeding in our hospital.

Objective

Primary objective

The primary objective was to determine the effectiveness of the combination mechanical thrombo-prophylaxis compared with pharmaco-mechanical thromboprophylaxis in reducing VTE incidence in major general surgical patients during the perioperative period.

Secondary objectives

Secondary objectives were to report adverse events such as readmission rate from VTE, all-cause mortality, complications of mechanical thromboprophylaxis, complications of pharmacologic thromboprophylaxis, and compliance with each prophylaxis method.

Materials and Methods

Study design

A single-center, prospective, randomized controlled study was conducted from 1 July 2018 and 31 December 2018 in the departments of general surgery in the general surgical ward and trauma and surgical critical care ward at Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. This study was conducted following the ACCP 2008 and 2012 Clinical Practice Guidelines.

This study was approved by the ethical committee of Ramathibodi Hospital approval; ID 09-61-03 COA.No. MURA 2018/644 and registered with the TCTR committee TCTR20210525006.

Participants

Eligible patients were those who were VTE high-risk patients (Caprini risk score ≥5) undergoing abdominopelvic surgery, the age of the patient was over 18 years old and providing informed consent. The exclusion criteria were the patients who were prescribed anticoagulants or history of DVT or peripheral arterial disease or glomerular filtration rate (GFR) less than 30 mL/min/1.73 m^2 or history of allergic to anticoagulants. Bilateral venous duplex ultrasonography (DUS) of the lower extremities was performed within 24 hours before surgery. The patients with preoperative DVT were excluded from the study.

Randomization

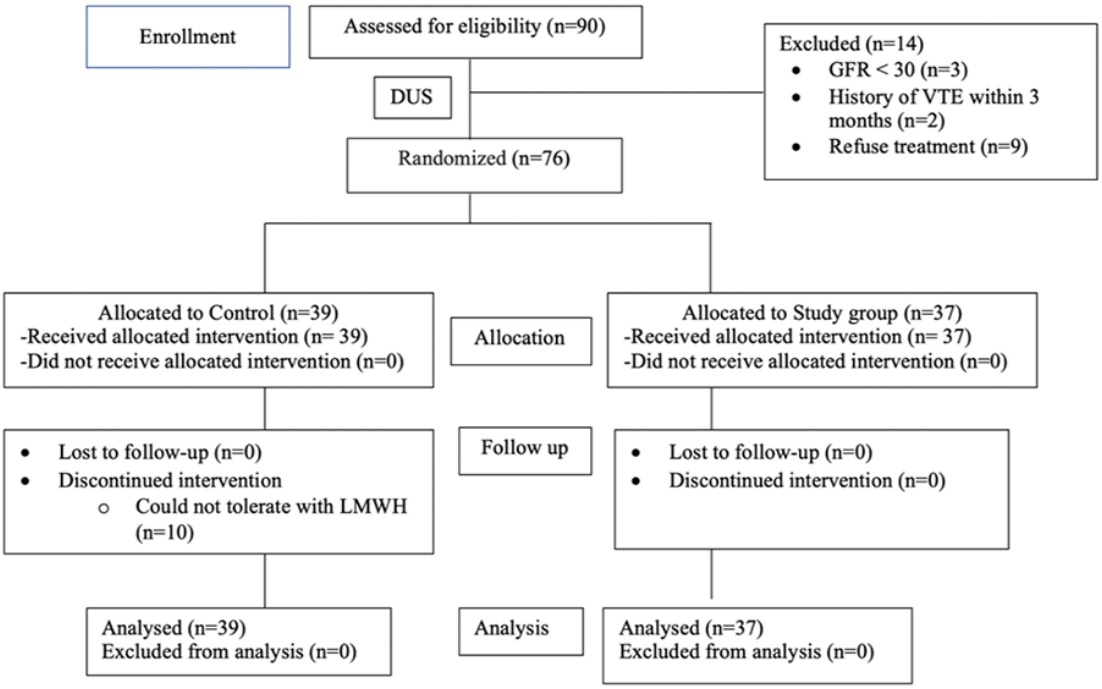
Randomization was performed with a 1: 1 allocation using computer-generated-block 4 randomizations by an independent statistician using STATA version 14.0. The treatment assignments were sealed in opaque envelopes, which were opened by an independent statistician who was on call after the patients were admitted. Figure 1 summarised the design of the study.

Blinding

Neither patients nor surgeons were blinded to the intervention due to obvious constrain. However, DVT and PE were the objective outcomes of this study. DVT was diagnosed by duplex ultrasound criteria which were uncompressible deep vein. Pulmonary embolism was diagnosed by computed tomographic pulmonary angiography.

Intervention group (IPC+GCS)

On the day of admission, before undergoing major abdominopelvic surgery, all patients routinely received GCS and IPC. We used class II GCS below knee level and IPC which covered the patient's lower extremities (Kendall SCD™ express sequential compression system, CardinalHealth™, Dublin, OH). The patients wore IPC and GSC before starting the operation, during intraoperative and postoperative periods. During the postoperative period, patients also applied GCS and IPC devices continuously until the patient could fully ambulate or discharge. Patients were judged to be fully ambulatory when they could walk



GFR = glomerular infiltration rate (mL/min/1.73 m^2)

Figure 1. CONSORT diagram, including enrollment and outcomes.

without assistance and could spend most of the day out of bed. The device was continued at least 18 hours per day.

Control group (IPC+GCS+LMWH)

The same protocol using IPC and GCS was applied to the control group. The patients were assigned to receive subcutaneous injections of enoxaparin 40 mg once daily, stopped before initial incision 12 hours, and restarted enoxaparin 40 mg. once daily from postoperative day 5^{th} to day 28^{th}.

Cointervention

All patients were assessed routinely daily by the nurse and surgeon for clinical VTE and complications of VTE prophylaxis. We encouraged the patients to early mobilization.

Outcomes

The primary outcome was VTE. The VTE surveillance protocol after surgery was a daily observation of clinical DVT and pulmonary embolism (PE). Postoperative screening venous DUS of lower extremities within 7 days or before patients were discharged from the hospital was obtained. Assessment of pulmonary embolism symptoms (PE) included dyspnea, desaturation, tachypnea, tachycardia, or chest pain. If clinical PE was suspected, the diagnosis was confirmed using computed tomography angiography. The VTE surveillance protocol after discharge, the patients were followed up at 28^{th} to 35^{th} days after surgery looking for the manifestations of DVT, PE, and adverse events and performing a venous duplex ultrasound of lower extremities.

The secondary outcomes were bleeding and complications from medical devices. Major bleeding was defined as the event that met at least one of the following criteria: resulted in death; clinically overt (required transfusion of at ≥2 units of packed red blood cells or whole blood, or decreased hemoglobin levels by at least 2 g/dL): retroperitoneal, intracranial and intraocular bleeding, bleeding required surgical or medical intervention to control the event.

Minor bleeding was defined as the events that did not meet any of the major bleeding criteria but resulted in one of the following: epistaxis lasting ≥5 minutes or epistaxis that required treatment, ecchymosis or hematoma ≥5 cm diameter, hematuria not associated with a urinary catheter, gastrointestinal hemorrhage not related to intubation or nasogastric tube placement, and subconjunctival hemorrhage requiring treatment or discontinuation of the anticoagulant.

Adverse events and complications of IPC and GCS were sensory impairment of the lower extremity due to nerve entrapment from GCS, allergy to stocking material, and skin irritation.

Sample size calculation

Based on the literature review, the incidence of asymptomatic VTE in this high-risk population was estimated to be 20%[7]. The sample size calculation assumed 80% statistical power to detect a 50% reduction in the incidence of VTE and using a continuity corrected χ^2 test of equal proportions with α=0.05, the calculation yielded 220 subjects per treatment arm. Assuming an attrition rate not to exceed 30%, a total of 315 patients were assigned to each of the treatment groups. Although the predetermined goal was 630 study patients, the enrollment was terminated early at 76. Several factors contributed to the decision to stop enrollment early. First, it took quite a long time to receive an institutional review board (IRB) by the medical ethics committee of Ramathibodi hospital. Second, the enrollment rate was decreased due to the limited time to study and the number of abdominopelvic surgeries.

Statistical analysis

Categorical variables reported as counts and percentages were compared using the Chi-squared test or Fisher exact test according to the sample size. Continuous variables reported as means$\pm$SD were compared using the unpaired t-test for normal distribution. Non-normal distribution variables reported as median and interquartile range were compared using the Mann-Whitney test. The p-value less than 0.05 was considered statistically significant. All analyses presented by intention-to-treat. We compared overall event rates using an intention-to-treat analysis for the relative risk. The analyses were performed using STATA version 14.0.

Results

Ninety patients were approached for eligibility at the surgical department, Ramathibodi Hospital, Bangkok, Thailand from July 2018 to December 2018. Seventy-six patients were allocated to the control and the study group. Thirty-nine patients were randomly assigned to the control group and 37 to the study group. In the control group, 10 cases discontinued the intervention whereas in the study group all patients followed the protocol.

Demographics and clinical characteristics of patients assessed for VTE risk were not statistically significant except the mean Caprini score and history of the central venous catheter which in the study group was higher than the control group as in Table 1. The mean age was 61$\pm$55 years and there was no history of VTE in both groups. Most of the patients (84.3%) had a history of cancer. The baseline characteristics of cancer were shown in Table 2. The most common cancer in this study was colorectal cancer. Mean cancer size was 4 cm and the majority of cancers was in stage 2 and 3. There was no significant difference between the two groups in the details of the procedures and related events as shown in Table 3.

For VTE prophylaxis details were shown in Table 4. Ten patients of the control group discontinued the intervention postoperatively between days 8 to 28 due to poor compliance using enoxaparin subcutaneously daily. Contrary to the study group, there was no patient discontinued the intervention. The durations of IPC and GCS usage were significantly higher in the study group and there was no complication of IPC in both groups. No bleeding complication from anticoagulant occurred. In the present study, there was neither case of readmission from VTE nor

Table 1. Baseline demographics and characteristics of the intention to treat population who were underwent abdominopelvic surgery

Characteristics	Study (n=37)	Control (n=39)	p-value
Male, n (%)	16 (43.2)	19 (48.7)	0.632
Age (years), mean (SD)	61.9 (13.7)	61.2 (15.4)	0.838
BMI (kg/ml^2), median (IQR)	24 (21 to 27)	24 (22 to 26)	0.647*
COPD, n (%)	3 (8.1)	4 (10.3)	0.999**
Oral contraception, n (%)	7 (18.9)	5 (12.8)	0.466
Hormonal therapy, n (%)	1 (2.7)	0 (0.0)	0.487
History of central venous catheter, n (%)	9 (24.3)	3 (7.7)	0.047
Previous VTE, n (%)	0 (0.0)	0 (0.0)	-
Previous Cancer, n (%)	30 (81.1)	32 (82.1)	0.913
Surgery for cancer, n (%)	32 (86.5)	32 (82.1)	0.596
Varicose vein, n (%)	23 (62.2)	24 (61.5)	0.955
Caprini score, mean (SD)	9.0 (2.1)	7.9 (1.7)	0.021

BMI = body mass index; COPD = chronic obstructive pulmonary disease; IQR = Interquartile range; SD = standard deviation; VTE = Venous thromboembolism

* Mann-Whitney U Test, ** Fisher's exact test

Table 2. Disease characteristics in cancer patients

Characteristics	Study (n=32)	Control (n=32)	p-value
Primary cancer, n (%)			
Colorectal cancer	24 (75.0)	30 (93.8)	0.172**
Stomach cancer	3 (9.4)	2 (6.3)	
Esophagus	1 (3.1)	0 (0)	
Hepatobiliary pancreatic cancer	2 (6.3)	0 (0)	
Gynecologic cancer	2 (6.3)	0 (0)	
Staging, n (%)			
I	4 (12.5)	1 (3.1)	0.303**
II	2 (6.3)	5 (15.6)	
III	17 (53.1)	20 (62.5)	
IV	9 (28.1)	6 (18.8)	
Tumor size (cm), median (IQR)	4 (2 to 5)	4 (3 to 5)	0.652*

IQR = Interquartile range
* Mann-Whitney U test, ** Fisher's exact test

Table 3. Detail of procedures

Characteristics	Study (n=37)	Control (n=39)	p-value
Type of operation, n (%)			
Laparotomy	26 (70.3)	19 (48.7)	0.056
Laparoscopy	11 (29.7)	20 (51.3)	
EBL (mL), median (IQR)	100 (200 to 500)	100 (50 to 150)	0.764*
General anesthesia, n (%)	37 (100.0)	39 (100.0)	-
Position, n (%)			
Supine	21 (56.8)	23 (59.0)	0.999
Lithotomy	16 (43.8)	16 (41.0)	
Hospital stay (day), median (IQR)	8 (5 to 13)	7 (6 to 9)	0.154*

EBL = Estimate blood loss; IQR = Interquartile range
* Mann-Whitney U test

an all-cause of death.

Five patients developed VTE (6.58%) in the present study and all of the VTE cases were asymptomatic DVT. All VTE cases were cancer patients. None of the patients developed PE. In the study group, 4 patients (10.8%) developed DVT, one of asymptomatic proximal DVT and 3 of asymptomatic calf vein DVT. One patient (2.6%) in the control group developed asymptomatic proximal DVT. The unadjusted relative risk (RR) was 4.22 (95% CI, 0.49 to 36.00, p=0.194). In both groups, 2 cases of asymptomatic proximal DVT occurred within postoperative day 3 when the pharmacological prophylaxis could not be given. So, in that period, the patients in both groups received only mechanical thromboprophylaxis. The details of VTE incidence were reported in Table 5. There was no new DVT developed in both groups during the follow-up period 8th to 28th days. The details of VTE cases were listed in Table 6.

Discussion

From the literature review, more than 20% of all post-operative hospitalized patients were at risk for VTE[8]. These surgical patients are a unique population who possess all 3 components of the Virchow triad (stasis, hypercoagulability, and endothelial injury) leading to thrombus formation. VTE has been known as a preventable cause of death in surgical patients. The American College of Chest Physicians (ACCP) 2012 guideline[1] stated recommendations, accessing VTE risk stratification and providing the thromboprophylaxis according to the risk of VTE. The patients undergoing surgery for cancer were at

Table 4. Details of VTE prophylaxis

Characteristics	Study (n=37)	Control (n=39)	p-value
Duration of IPC usage (days), median (IQR)	3 (2 to 3)	2 (2 to 2)	<0.001*
Duration of GCS (days), median (IQR)	4 (3 to 5)	3 (3 to 4)	0.003*
Protocol adherence[+], n (%)	37 (100)	29 (74.4)	0.001
Complication of IPC, n (%)	0 (0)	0 (0)	-
Complication of enoxaparin n (%)	0 (0)	0 (0)	-
Bleeding events, n (%)			
Minor bleeding[++]	0 (0)	0 (0)	-
Major bleeding[+++]	0 (0)	0 (0)	

GCS = Graduated compression stockings; IPC = Intermittent pneumatic compression; IQR = Interquartile range; VTE = Venous thromboembolism

[+] Protocol adherence is defined by receiving anticoagulant for 28 days after surgery in the control group and receiving IPC and GCS until good ambulation in the study group.

[++] Major bleeding was defined as the event that met at least one of the following criteria: resulted in death; clinically overt (required transfusion of at ≥2 units of packed red blood cells or whole blood, or decreased hemoglobin levels by at least 2 g/dL): retroperitoneal, intracranial and intraocular bleeding, bleeding required surgical or medical intervention to control the event.

[+++] Minor bleeding was defined as the events that did not meet any of the major bleeding criteria but resulted in one of the following: epistaxis lasting ≥5 minutes or epistaxis that required treatment, ecchymosis or hematoma ≥5 cm diameter, hematuria not associated with a urinary catheter, gastrointestinal hemorrhage not related to intubation or nasogastric tube placement, and subconjunctival hemorrhage requiring treatment or discontinuation of the anticoagulant.

* Mann-Whitney U test

Table 5. Outcome: Incidence of VTE in post-operative period 1st to 7th day

Characteristics	Study (n=37)	Control (n=39)	Relative risk (95% CI)	p-value
VTE, n (%)	4 (10.8)	1 (2.6)	4.22 (0.49 to 36)	0.194
Proximal DVT	1 (2.7)	1 (2.6)	1.05 (0.07 to 16.24)	0.999
Calf vein DVT	3 (8.1)	0 (0)	-	-
Symptomatic PE	0 (0)	0 (0)	-	-

DVT = Deep vein thrombosis; PE = Pulmonary embolism; VTE = Venous thromboembolism

extremely high risk for VTE[9,10].

We studied the high-risk VTE population. From baseline characteristics, all patients had a Caprini score more than or equal to 5 and most of the patients were malignancy accounted for 84.2%. The Caprini score and history of central venous catheterization were higher in the study arm than the control arm. The type of operation, in the study group, had a higher rate of laparotomy than in the control group. Due to the design of the study was a randomized controlled study, the difference between these two groups might be by chance.

From the ENDORSE study[11], there was 59% of surgical high-risk patients received ACCP-recommended VTE prophylaxis, especially in Thailand, the rate of at-risk surgical patients receiving ACCP- recommended prophylaxis was only 0.2%. There were three main factors, the first was surgeons concerned about bleeding complications especially fatal bleeding when patients received pharmacological prophylaxis. Although Asian venous thromboembolism guidelines reviewed that major bleeding rates were less than 1% following pharmacological prophylaxis with either LMWH or the new oral anticoagulants[8]. The result of our study confirmed the low rate of pharmacological prophylaxis in the Thai population which was no case of bleeding in the controlled arm.

The second reason was the lack of awareness regarding VTE even though the high incidence of VTE, DVT, PE, and fatal PE in non-VTE-prophylactic colorectal surgery ranged from 0.18 to 42.0%[12-15]. The third reason was poor compliance during discharge to 28 days of LMWH injected subcutaneous daily in cancer group. It was recommended that patients with cancer who underwent an operation received anticoagulation for up to 4 weeks postoperatively[1,9,10]. From our study, the rate of non-adherence in the control group was high accounted for 10 of 39 patients (25.6%). These due to the patients in the control

Table 6. Characteristic of postoperative acute DVT

Case No.	Age (years)	Caprini score	Time of Diagnosis (post-op)	Duration of surgery (min)	Position during surgery	Type of operation	Organ	Type of cancer	Staging	Symptom	Site of DVT
Control group (anticoagulant combined with IPC and GCS)											
1	78	12	Day 3	200	Supine	Open	Colon	Adeno CA	III	Asymptomatic	Lt CFV+Pop V
Study group (IPC combined with GCS)											
1	60	12	Day 3	150	Lithotomy	Open	Endometrium	Adeno CA	IV	Asymptomatic	Lt CFV + Pop V
2	84	13	Within 3 to 7 day	75	Supine	Open	Rectum	Adeno CA	IV	Asymptomatic	Rt. Anterior tibial vein
3	61	8	Within 3 to 7 day	245	Lithotomy	Lap	Rectum	Adeno CA	I	Asymptomatic	Rt. Anterior tibial vein
4	73	10	Within 3 to 7 day	245	Lithotomy	Open	Rectum	Adeno CA	III	Asymptomatic	Lt. Anterior tibial vein

CA = carcinoma; CFV = common femoral vein; DVT = deep vein thrombosis; Pop V = popliteal vein; Lt = left; Rt = right; Open = Laparotomy; Lap = laparoscopy; IPC = intermittent pneumatic compression; GCS = graduated compressive stocking

group did not convenient to inject LMWH injection subcutaneously until 28 days post-operation because of pain and bruise. These resulted in the preferred use of only mechanical prophylaxis during hospitalization as a VTE prevention for surgical patients in Thailand.

In the present study, randomized patients who underwent abdominopelvic surgery compared the method of VTE prophylaxis between IPC+GCS and IPC+GCS+ LMWH. The results were no significant in VTE incidence, but in IPC+GCS group trended to higher incidence of VTE than in IPC+GCS+LMWH group, 4 (10.8%) vs. 1 (2.6%); unadjusted RR 4.22, 95% CI 0.49 to 36.00, p-value=0.194). This might be due to the low number of enrolled patients. We expected 630 study patients but we could enroll 76 patients. If we collected more patients, there would have some differences between these two groups. Another issue was the high non-adherence to the protocol in the control group that might affect the outcome. There was neither bleeding complication nor complication from IPC occurred. The important finding was all VTE cases were asymptomatic DVT which was found from screening duplex ultrasound within 7 days, after that there was no VTE case was found. One case of proximal VTE was found equal in both groups (2.7% vs. 2.6%, RR 1.05; 95% CI 0.07 to 16.24, p-value=0.999). All asymptomatic proximal DVT cases occurred in 3 day-postoperative periods in which the patients in both groups were not received LMWH. We suggested anticoagulation should be resumed within three days or as soon as possible after surgery.

All three asymptomatic calf vein DVT cases that occurred in the control group (8.1%) were detected between postoperative days 3 to 7. It might be concluded that mechanical thromboprophylaxis (IPC+GCS) was ineffective to prevent DVT especially in cancer surgery in high-risk patients (Caprini score ≥5). For calf vein DVT, ACCP 2016[16] suggested the following as risk factors for extension of distal DVT that favored anticoagulation over surveillance: (1) D-dimer is positive; (2) thrombosis is extensive; (3) thrombosis is close to the proximal veins; (4) there is no reversible provoking factor for DVT; (5) active cancer; (6) history of VTE, and (7) inpatient status. So, all calf vein DVT cases in our study which were active cancer patients and inpatients status should be treated with anticoagulants. We suggested that in case of contraindication for pharmacological prophylaxis in cancer surgery, the patients should be resumed anticoagulant as soon as possible or performed a duplex ultrasound on the seventh-day post-operation or before discharge to detect DVT.

From the RIETE registry, they observed symptomatic VTE in abdominopelvic cancer. Fifty-two percent of VTE patients presented with pulmonary embolism. Most VTE cases (84%) were detected after the first postoperative week and 38% after one month. VTE presented after hospital discharge in 54% of cases[17]. Contrary to our study, no patient had VTE after discharge. According to the protocol of the study, we aggressively screened DVT in all patients during preoperative, early postoperative, and

before discharge. We found all of the VTE cases were asymptomatic so we could detect all VTE cases that occurred in the hospital. This might explain why we had no VTE patients after hospital discharge from duplex ultrasound screening in both groups.

The limitations of this study were the low number of enrolled patients and the high number of non-adherences in the control group (25.6%). This represented that some cancer patients could not adhere to LMWH subcutaneously until the 28th-day post-operation as ACCP recommendation.

Conclusion

The effectiveness of IPC combined with GCS was not superior to pharmaco-mechanical thromboprophylaxis for VTE prevention in high-risk surgical patients. Neither bleeding complication from anticoagulant nor medical device-related pressured injury occurred. Our suggestions were to resume LMWH within 3 days after surgery or as soon as possible. If the patients had contraindication for LMWH, duplex ultrasound should be performed on the 7th day or before discharge for detecting DVT.

What is already known on this topic?

Mechanical prophylaxis has been less effective than pharmacological prophylaxis in VTE prophylaxis for surgical patients. Intermittent pneumatic compression has become the standard method in high-risk bleeding patients.

What this study adds?

A combination of intermittent pneumatic compression and graduated compressive stocking was not superior to pharmaco-mechanical thromboprophylaxis for VTE prevention in high-risk surgical patients.

Acknowledgements

The authors gratefully acknowledged Nipapan Choonu for the statistical analysis.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. 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.
2. 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.
3. Turpie AG, Bauer KA, Caprini JA, Comp PC, Gent M, Muntz JE. Fondaparinux combined with intermittent pneumatic compression vs. intermittent pneumatic compression alone for prevention of venous thromboembolism after abdominal surgery: a randomized, double-blind comparison. J Thromb Haemost 2007;5:1854-61.
4. Sachdeva A, Dalton M, Amaragiri SV, Lees T. Elastic compression stockings for prevention of deep vein thrombosis. Cochrane Database Syst Rev 2010;(7): CD001484.
5. 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.
6. 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.
7. Feng JP, Xiong YT, Fan ZQ, Yan LJ, Wang JY, Gu ZJ. Efficacy of intermittent pneumatic compression for venous thromboembolism prophylaxis in patients undergoing gynecologic surgery: A systematic review and meta-analysis. Oncotarget 2017;8:20371-9.
8. Liew NC, Moissinac K, Gul Y. Postoperative venous thromboembolism in Asia: a critical appraisal of its incidence. Asian J Surg 2003;26:154-8.
9. Anderson DR, Morgano GP, Bennett C, Dentali F, Francis CW, Garcia DA, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv 2019;3:3898-944.
10. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol 2020; 38:496-520.
11. Cohen AT, Tapson VF, Bergmann JF, Goldhaber SZ, Kakkar AK, Deslandes B, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet 2008;371:387-94.
12. Yang SS, Yu CS, Yoon YS, Yoon SN, Lim SB, Kim JC. Symptomatic venous thromboembolism in Asian colorectal cancer surgery patients. World J Surg 2011; 35:881-7.
13. Choi S, Lee KW, Bang SM, Kim S, Lee JO, Kim YJ, et al. Different characteristics and prognostic impact of deep-vein thrombosis/pulmonary embolism and intraabdominal venous thrombosis in colorectal cancer patients. Thromb Haemost 2011;106:1084-94.
14. Weida D, Patrick LY, Andrew YW. Is it safe to perform operation for colorectal malignancy in Chinese patients without DVT prophylaxis? An 8-year experience from a regional hospital in Hong Kong. Chin Med J (Engl) 2010;123:1973-5.
15. Ho YH, Seow-Choen F, Leong A, Eu KW, Nyam D,

Teoh MK. Randomized, controlled trial of low molecular weight heparin vs. no deep vein thrombosis prophylaxis for major colon and rectal surgery in Asian patients. Dis Colon Rectum 1999;42:196-202; discussion 202-3.
16. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE Disease: CHEST guideline and expert panel report. Chest 2016;149:315-52.
17. Bustos Merlo AB, Arcelus Mart□nez JI, Turi□o Luque JD, Valero B, Villalobos A, Aibar M, et al. Form of presentation, natural history and course of postoperative venous thromboembolism in patients operated on for pelvic and abdominal cancer. Analysis of the RIETE registry. Cir Esp 2017;95:328-34.