

 **Original Article** 

Characteristics of Symptomatic Pulmonary Thromboembolism among Postoperative and Hospitalized Patients

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Backgrounds: Pulmonary thromboembolism (PTE) is severe complication which may arise during all medical service. The purpose of this study is to evaluate inpatient symptomatic PTE.

Materials and Methods: From 2005 to 2016, we experienced 75 symptomatic PTE patients among 600 venous thromboembolism patients. According to the place of occurrence, patients were divided to inpatient group and outpatient group. We further divided inpatient group to surgical group and non-surgical group.

Results: Inpatients group, 38 had PTE (surgical: 23, non-surgical: 15). Outpatients group, 37 had PTE (with medical practice: 22, without medical practice: 15). Severity of PTE were follows; cardiac arrest 2, massive 13, sub-massive 18, non-massive 42. In surgical group, anticoagulation had been used in 3/23 (13.6%), intermittent pneumatic compression had been used in 16/23 (72.9%), compression stockings had been used in 20/23 (90.9%). In non-surgical group, no anticoagulation had not been used, intermittent pneumatic compression had been used in 2/15 (13.3%), compression stockings had been used in 2/15 (13.3%).

Conclusion: As PTE prophylaxis, anticoagulation had been scarcely used in surgical group. Delayed anticoagulation

may decrease symptomatic PTE in surgical patients. Despite adequate prophylaxis, PTE cannot be prevented completely. Medical staff and patients should recognize the risk of PTE together. (This is a translation of *Jpn J Phlebol* 2018; 29(1): 33–40.)

Keywords: venous thromboembolism, pulmonary thromboembolism, prevention

Introduction

The first “Japanese Guideline for Prevention of Venous Thromboembolism” was published in 2004.¹⁾ After the prevention fee of venous thromboembolism has been introduced, mechanical prevention has been widely used. But pharmacological prevention has not been widely used for fear of bleeding. The Japanese Society of Anesthesiologist reported that mechanical prevention decreased pulmonary thromboembolism (PTE) occurrence, and pharmacologic prevention decreased perioperative PTE death.²⁾ After all, PTE during medical service has still been encountered. We retrospectively reviewed our PTE cases that occurred during medical service (i.e., hospitalized and outpatient medical and surgical patients) and discussed forward and limit of PTE prevention.

Materials and Methods


We experienced 600 venous thromboembolism (VTE) patients from 2005 through 2016. Among them, we analyzed 75 (12.5%) symptomatic PTE patients. We divided them into inside of the hospital patients and outside of the hospital patients according to the occurrence of PTE. In addition, we divided patients inside of the hospital into surgical patients, those who experience PTE after operation of trauma, and non-surgical patients, those who experienced PTE during hospitalization for medical reason. Patients outside of the hospital were divided into patients under some medical service or under no medical service.

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In our institute, VTE risk assessment for surgical patient is mandatory for physicians but not for medical patients. So majority of the medical patients were not performed with VTE risk assessment. In addition, methods of VTE prevention are finally decided not only for the patient's VTE risk but also for the patient's skin and bleeding risk. So the adaptation of prevention methods is left to be a matter of physician's discretion. Highest-risk patient may be managed only with mechanical prevention.

Severity of PTE was categorized to cardiac arrest, massive, sub-massive, and non-massive, according to Guidelines for the Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis JCS 2009 (http://www.j-circ.or.jp/guideline/pdf/JCS2009_andoh_d.pdf).

Table 1 Characteristics of symptomatic PTE patients

Age	22–81 (average 60)	
Gender	Female; 38 (50.7%), Male; 37 (49.3%)	
Onset	Inside of the hospital; 38	Surgical; 23 (30.7%) Non-surgical; 15 (20.0%)
	Outside of the hospital; 37	With medical practice; 22 (29.3%) Without medical practice; 15 (20.0%)

Table 2 Risk factors of PTE patients

Risk factors	n (%)	n (%)
Malignant diseases	34 (45.3)	Pre-op 10 (29.4)
		Post-op 8 (23.5)
		Under chemotherapy 11 (32.4)
		Recurrent disease 5 (14.7)
Non-malignant disease post-op	14 (18.7)	
Cesarean section	3 (4)	
Post-op total	25 (33.3)	
Thrombophilia	6 (8)	
Paralysis	4 (5.3)	
Immobilization	4 (5.3)	
Hormone replacement therapy	4 (5.3)	
Idiopathic	2 (2.7)	
Others	1 (1.3)	Pneumonia 1 (1.3)
		Ulcerative colitis 1 (1.3)
		Varicose vein 1 (1.3)
		Fracture 1 (1.3)

Table 3 Severity of PTE patients

PTE severity	n	Death	With symptomatic DVT	Inside of the hospital Surgical (n=23)	Inside of the hospital Non-surgical (n=15)	Outside of the hospital With medical practice (n=22)	Outside of the hospital Without medical practice (n=15)
Cardiac arrest	2	2	0	2 (8.7%)	0	0	0
Massive	13	1	0	7 (30.4%)	2 (13.3%)	2 (9.1%)	2 (13.3%)
Sub-massive	18	0	5	5 (21.7%)	1 (6.7%)	8 (36.4%)	4 (26.7%)
Non-massive	42	0	13	9 (31.9%)	12 (80%)	12 (54.5%)	9 (60%)

Results

Entire cases

Characteristics of 75 symptomatic PTE patients are listed in **Table 1**. Thirty-eight of 75 patients showed PTE inside of the hospital (surgical: 23, non-surgical: 15). Thirty-seven of 75 patients showed PTE outside of the hospital (with medical practice including post-operative patients soon after discharge: 22, without medical practice: 15). Risk factors of VTE are listed in **Table 2**. In many cases, malignancies and operation are listed, followed by thrombophilia, paralysis, bed rest, and hormone replacement therapy. Severity of PTE according to onset and backgrounds is listed in **Table 3**. Majority of cardiac arrest and massive cases are seen in inside of the hospital surgical cases. On the other hand, sub-massive and non-massive cases are dominant.

Post-operative cases

Twenty-four PTE cases occurred inside of the hospital after surgery, and one PTE case occurred outside of the hospital soon after discharge were reviewed. Severity of PTE and department were listed in **Table 4**. Cardiac arrest was seen in each gastrointestinal surgery and orthopedic surgery. Many PTE cases were seen in these departments. VTE prophylaxis done at PTE occurrence was listed in **Table 5**. Although elastic stockings and intermittent pneumatic compression were adopted in many cases, prophylactic anticoagulation was used in few cases. Cardiac arrest occurred in two cases, in spite of prophylactic anticoagulation. We thought that PTE prophylaxis has a limit. Correlation of PTE severity and onset of post-operative day is listed in **Fig. 1**. Cardiac arrest cases occurred after the 9th post-operative day, whereas many of massive cases occurred before the 3rd post-operative day.

Inside of the hospital, non-surgical cases

Department and severity of PTE occurred inside of the hospital during medical service is listed in **Table 6**. Many PTE cases that were seen in gastroenterology and neurology may be due to cancer chemotherapy and complicated paralysis. VTE prophylaxis done at PTE occurrence is listed in **Table 7**. In addition to prophylactic anticoagulation, elastic stocking and intermittent pneumatic compression

Table 4 Severity of PTE (post-operative patients)

	Symptomatic PTE (24)	Cardiac arrest (2)	Massive (7)	Sub-massive (6)	Non-massive (9)
Gastrointestinal surgery	7	1	3	0	3
Orthopedics	7	1	3	0	3
Obstetrics	2	0	0	1	1
Gynecology	2	0	1	1	0
Neurosurgery	2	0	0	2	0
Urology	1	0	0	0	1
Thoracic surgery	1	0	0	0	1
Breast surgery	1	0	0	1	0
Cardiology	1	0	0	1	0

Table 5 VTE prevention (post-operative patients)

PTE	Operation (Disease)	Onset (POD)	ECS	IPC	AC
Cardiac arrest	Colon cancer perforation	13	+	—	—
Cardiac arrest	Spinal tumor	20	+	+	—
Massive	Inguinal hernia	1	+	—	—
Massive	Ovarian cancer	1	+	+	+
Massive	Laparoscopic cholecystectomy	2	+	—	—
Massive	Total hip replacement	2	+	+	—
Massive	Total hip replacement	2	+	+	+
Massive	Pelvic osteotomy	4	+	+	—
Massive	Rectal cancer	17	+	+	—
Sub-massive	Acute myocardial infarction	5	—	—	—
Sub-massive	Subarachnoid hemorrhage	27	+	—	—
Non-massive	Cesarean section	1	+	+	—
Non-massive	Cesarean section	1	+	+	+
Non-massive	Open cholecystectomy	2	+	+	—
Non-massive	Renal cell carcinoma	2	+	+	—
Non-massive	Cesarean section	3	+	+	—
Non-massive	Total hip replacement	3	+	+	—
Non-massive	Scoliosis surgery	6	+	+	—
Non-massive	Lung cancer	8	+	+	—
Non-massive	Esophageal cancer	14	—	—	—
Non-massive	Epidura hematoma	14	+	+	—
Non-massive	Retroperitoneal tumor	15	+	+	—
			+ (90.9%)	+ (72.9%)	+ (13.6%)

ESC: elastic compression stocking; IPC: intermittent pneumatic compression; AC: anticoagulation

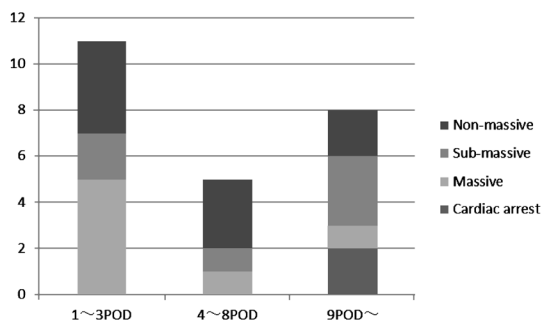


Fig. 1 Onset and severity of post-operative PTE patients.

sion were also used in few patients.

Outside of the hospital cases

Among 37 outside of the PTE cases, 22 were receiving any medical service and 15 were not. Outside-of-the-hospital cases under any medical service, excluding one post-operative case, who occurred PTE soon after discharge, is listed in Table 8. Among these cases, mild PTE was dominant similar with inside of the hospital non-surgical cases. Many patients were receiving chemotherapy or hormonal therapy, because of gastrointestinal, respiratory, genitourinary, and gynecological malignancies (Table 9).

Table 6 Severity of PTE (non-surgical patients)

Division	PTE (15)	Cardiac arrest (0)	Massive (2)	Sub-massive (1)	Non-massive (12)
Gastrointestinal	4	0	0	0	4
Neurology	4	0	2	0	2
Respiratory	2	0	0	1	1
Endocrine	2	0	0	0	2
Genital	1	0	0	0	1
Head and neck	1	0	0	0	1
Connective tissue	1	0	0	0	1

Table 7 VTE prevention (non-surgical patients)

PTE	Operation (Disease)	ECS	IPC	AC
Massive	Brain tumor	—	—	—
Massive	Intra cranial hemorrhage	+	+	—
Sub-massive	Antiphospholipid syndrome	—	—	—
Non-massive	Chemotherapy for lung cancer	—	—	—
Non-massive	Reccurence of pancreatic cancer	—	—	—
Non-massive	Chemo-radio therapy for esophageal cancer	—	—	—
Non-massive	Advanced colon cancer	—	—	—
Non-massive	Ulcerative colitis	—	—	—
Non-massive	Brain tumor	—	—	—
Non-massive	Ovarian tumor	—	—	—
Non-massive	Parotid gland tumor	—	—	—
Non-massive	Pituitary Cusing syndrome	—	—	—
Non-massive	Autoimmune hypophysitis	—	—	—
Non-massive	Pemphigus	—	—	—
Non-massive	Arterio-venous fistula of lumbar spine	+	+	—
		+ (13.3%)	+ (13.3%)	+ (0%)

ESC: elastic compression stocking; IPC: intermittent pneumatic compression; AC: anticoagulation

Table 8 Severity of PTE (outpatients under medical treatment)

Division	PTE (21)	Cardiac arrest (0)	Massive (2)	Sub-massive (4)	Non-massive (15)
Gastrointestinal	5	0	0	0	5
Respiratory	5	0	0	2	3
Male genital system	4	0	0	2	2
Female genital system	3	0	0	0	3
Orthopedics	1	0	1	0	0
Neurology	1	0	0	0	1
Cardiology	1	0	1	0	0
Hematology	1	0	0	0	1

Discussion

In 2004, Japanese guideline for prevention of venous thromboembolism was published,¹⁾ since then, VTE has been well recognized, and mechanical prevention has been widely used coupled with establishment of prevention fee. Since 2004, perioperative PTE decreased because of induction of mechanical prevention, and perioperative PTE death also decreased because of induction of pharmacologic prevention.²⁾ Although perioperative mechanical prevention has been widely used, new parenteral throm-

boprophylaxis (low molecular weight heparin and factor Xa inhibitor, which could not be used in Japan 2004) became available for orthopedic and abdomino-pelvic surgery, oral factor Xa inhibitor became available for orthopedic surgery, which result in great concern about pharmacologic prevention, we sometimes meet with perioperative symptomatic PTE. Furthermore, VTE risk assessment for medical patients has not been popular, because of its complexity. Previously we reported in hospital surgical and non-surgical VTE patients.³⁾ We considered that for surgical patients, pharmacologic prophylaxis

Table 9 VTE prevention (outpatients under medical treatment)

PTE	Disease	Risk factors	ECS	IPC	AC
Sub-massive	Advanced lung cancer	Malignant diseases (13/21, 61.9%)	—	—	—
Sub-massive	Prostate cancer, Chemotherapy	Chemotherapy, Hormonal therapy (8/21, 38.1%)	—	—	—
Sub-massive	Prostate cancer, Hormonal therapy		—	—	—
Sub-massive	Ovarian cancer, Chemotherapy		—	—	—
Sub-massive	Recurrent ovarian cancer		—	—	—
Non-massive	Colon cancer		—	—	—
Non-massive	Bile duct cancer, Breast cancer		—	—	—
Non-massive	Metastatic prostate cancer, Hormonal therapy		—	—	—
Non-massive	Recurrent bile duct cancer, Chemotherapy		—	—	—
Non-massive	Recurrent rectal cancer, Chemotherapy		—	—	—
Non-massive	Prostate cancer, Chemotherapy		—	—	—
Non-massive	Prostate cancer, Hormonal therapy		—	—	—
Non-massive	Bone marrow transplantation Donor, Pelvic tumor		—	—	—
Sub-massive	Dysmenorrhea, Hormone replacement therapy	Hormonal therapy (3/21, 14.3%)	—	—	—
Non-massive	Interstitial pneumonia, Steroid therapy		—	—	—
Non-massive	Interstitial pneumonia, Steroid therapy		—	—	—
Sub-massive	Atypical mycobacteriosis	Immobilization (1/21, 4.8%)	—	—	—
Non-massive	Pancreatic pseudocyst	Infectious disease (1/21, 4.8%)	—	—	—
Massive	Venous aneurysm of popliteal vein	Venous aneurysm (1/21, 4.8%)	—	—	—
Massive	Achilles tendon rupture, Cast	Cast (1/21, 4.8%)	—	—	—
Non-massive	Brain infarction, Paralysis	Paralysis (1/21, 4.8%)	—	—	—

ESC: elastic compression stocking; IPC: intermittent pneumatic compression; AC: anticoagulation

should be used after hemostasis, because many symptomatic VTE occurred among “high risk” patients. We also considered that for non-surgical patients, induction of VTE risk assessment and regular re-assessment, followed by appropriate prophylaxis are important.

In Japan, mechanical prophylaxis has been widely used, because of its low complication rate. In contrast, pharmacologic prophylaxis has not been widely used, because it has risk of bleeding and cannot be claimed under Japanese DPC system. Therefore, pharmacologic prophylaxis is used in only a few aggressive hospital for limited patients. In ACCP guideline 2012, it is described that optimal thromboprophylaxis in nonorthopedic surgical patients will consider the risks of VTE and bleeding complications as well as the values and preferences of individual patients.⁴⁾ VTE risk estimate is more intelligible than bleeding risk estimate, because bleeding risk vary from operative procedure, many patients' factors, i.e., obesity. It is reported that increase in surgical duration is directly associated with an increase in the risk of VTE.⁵⁾ On the other hand, increase in surgical duration is also associated with an increase in risk of bleeding.^{6,7)} Because conclusive assessment of VTE and bleeding risk is hard to decide, many surgeons may avoid pharmacologic prophylaxis for fear of bleeding rather than VTE. In Japanese guidelines, some additional risks are listed in addition to basic risks, which may assist surgeons' decision. Rogers score and Caprini score may be helpful to decide pharma-

colgic prophylaxis, although they were made for patients in western countries not for Japanese.⁸⁻¹⁰⁾ In this study, pharmacologic prophylaxis had been used in only 13.6% of PTE patients. Two cardiac arrest patients arise from no pharmacologic prophylaxis group. One developed PTE 13 days after surgery for perforation with colon cancer, and the other developed PTE 20 days after surgery for spinal cord tumor. Pharmacologic prophylaxis might be safely used in both cases, because several days passed from surgery. On the other hand, 2 massive PTE occurred in spite of pharmacologic prophylaxis. We should recognize that there is a limit of PTE prophylaxis. Perioperative VTE risk continues not only some days but also several months after operation.^{11,12)} In this study, 2 cases developed cardiac arrest PTE after 9th post-operative day. Pharmacologic prophylaxis several days after surgery with sure hemostasis may reduce these delayed VTE. Those who is not able to be anticoagulated, D-dimer testing and/or periodic surveillance with venous compression ultrasound may be helpful. If proximal deep vein thrombosis was detected, retrievable inferior vena cava filter may be inserted with early retrieve in order to avoid filter thrombosis or fracture.¹³⁾

Symptomatic PTE occurs in patients with much medical illness (i.e., cancer chemotherapy), prevention of VTE for those patients are also important.¹⁴⁾ As VTE is a major complication of cancer, ASCO guideline recommend that hospitalized patients who have active malignancy with acute medical illness of reduced mobility should receive

pharmacologic thromboprophylaxis in the absence of bleeding or other contraindication.¹⁵⁾ Hospitalization is recognized a risk of VTE, so VTE risk assessment should be performed at admission. Medical accident investigation and support center, Japan Medical Safety Research Organization published “Analysis of deaths related to Acute Pulmonary Thromboembolism” in August 2017 (https://www.medsafe.or.jp/uploads/uploads/files/teigen_02english.pdf). In the recommendations, it is mentioned that “it is important to grasp the possible risks of developing acute PTE in hospitalized patients.” But prophylaxis rate among medical patients is lower than surgical patients, may be because of complexity of risk assessment of medical patients.¹⁶⁾

In Japanese guideline, differ from assessment of surgical patients, those of medical patients is consisted from in combination from basic risk and acute risk, in which each have “strong,” “medium,” and “weak” risks. In contrast to VTE risk assessment of surgical patients, those of medical outpatients are complex. Although apoplectic stroke is strong VTE risk among acute phase risk, cerebral hemorrhage and hemorrhagic cerebral infarction are contraindication of pharmacologic thromboprophylaxis, so mechanical prophylaxis is recommended. In this study, 2 massive PTE patients arise from non-surgical patients. They were suffering from cerebral hemorrhage and brain tumor, pharmacologic prophylaxis were hesitated. Although adequate mechanical prophylaxis had been used, massive PTE occurred in the cerebral hemorrhage case. We consider that VTE prophylaxis has a limit. In the “Analysis of deaths related to Acute Pulmonary Thromboembolism,” prevention with patient participation is recommended. In view point of medical safety, health care professionals and patients should share the risk that PTE may occur in spite of VTE prevention.

Recently, cancer chemotherapy increase including neoadjuvant, adjuvant in addition to recurrent cases. Especially, outpatient chemotherapy increase, VTE prevention for outpatients is important together with non-surgical medical patients. Chemotherapy is reported a risk of cancer-related VTE.^{17–20)} VTE risk of cancer patients increase and vary according to patients’ condition such as epithelial injury of chemotherapy, hypercoagulability from appetite loss and dehydration, venous stasis from immobility.

In this study, 21 of 37 outpatients’ PTE had been under medical practice. Any of these patients were used any VTE prophylaxis. Twelve of these 21 were with active cancer, VTE prophylaxis for outpatients’ cancer patients are urgent. Though ASCO guideline does not recommend routine pharmacologic prophylaxis, high risk cancer patients receiving chemotherapy might receive pharmacologic prophylaxis on a case-by-case basis.¹⁵⁾ As the first

step, patients’ instruction and risk assessment of VTE such as appetite loss, dehydration, immobilization, and cancer status, may be conducted.

In Japan, since first publish of VTE prevention guideline, perioperative PTE has been decreased. To achieve more reduction of perioperative PTE, delayed pharmacologic prophylaxis induction after hemostasis, screening D-dimer testing and/or compression ultrasonography for patients with high bleeding risk, may be effective. For hospitalized medical patients, VTE risk assessment should be performed for all patients in admission, and adequate thromboprophylaxis should be conducted. For high risk outpatients, VTE instruction followed by proactive practice prophylactic actions may be actual. In United States, ahead of our country, ASCO provides VTE prophylaxis guideline; VTE prophylaxis for cancer patients is great concern. As is in United States, VTE prophylaxis guideline for cancer patients should be provided based on Japanese data.

Although medical related PTE may not be prevented completely because of the illness itself and limited medical service, we should advance VTE prophylaxis to reduce PTE according with listed provisions, in each institute.

Conclusion

In post-operative PTE patients, pharmacologic prophylaxis was less employed. Post-operative PTE may be reduced by using pharmacologic prophylaxis in consideration of bleeding risk and delayed use. In hospitalized medical patients, PTE may be reduced by induction of VTE risk assessment and appropriate prophylaxis. VTE prevention for cancer patients, Japanese original guideline should be provided based of evidence.

Disclosure Statement

There is no conflict of interest for this article.

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