



Safety of early orthopedic surgery in patients with intermediate/low- or low-risk pulmonary embolism

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Background: Preoperative pulmonary embolism (PE) is one of the comorbidities in patients with hip fracture. However, previous studies have not identified the optimal timing of surgery in these patients, who might require early surgery. This study aimed to investigate the safety and clinical feasibility of early surgery in patients with hip fracture and acute PE.

Methods: The medical records of 156 patients with hip fracture, who were suspected to have PE and underwent pulmonary computed tomography angiography at Asan Medical Center from January 2008 to December 2017, were retrospectively reviewed. After excluding patients who were diagnosed with PE during the postoperative period, the baseline characteristics and clinical course were compared between patients preoperatively diagnosed with PE (PE group) and patients without PE during the hospital stay (non-PE group). Adverse outcomes were evaluated during 3 months postoperatively.

Results: The baseline characteristics were not different between the PE group (n=90) and the non-PE group (n=50). All patients in the PE group were classified as having an intermediate/low or low risk according to the European Society of Cardiology guidelines and underwent surgery within 30 days after the PE diagnosis (median duration: 2 days). None of the patients in both groups developed symptomatic venous thromboembolism (VTE) during the follow-up. Moreover, there were no statistically significant differences in major bleeding, clinically relevant nonmajor (CRNM) bleeding, transfusion amount, bleeding site, and length of hospital stay between the PE and non-PE groups.

Conclusions: Our results suggest that early surgery might be a reasonable treatment option in patients with hip fracture and acute PE.

Keywords: Hip fracture; surgery; pulmonary embolism (PE); venous thromboembolism (VTE); safety

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Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a relatively common condition with increasing incidence and prevalence worldwide (1-3). Although new classes of drugs, such as direct oral anticoagulants (DOACs), have been effectively used for its prevention and treatment (4,5), VTE is still associated with significant morbidity and mortality (6).

There are several risk factors for the development of VTE. Approximately 20–30% of all PE events are associated with other factors including trauma, major surgery, and recent immobilization (7,8). Among these identifiable risk factors, fracture that requires surgery is associated with the development of VTE during both the preoperative and postoperative periods (9-11). Generally, it is recommended to postpone elective surgery for a minimum of 2–4 weeks from the acute PE event because of the high risk of recurrence in the first 4 weeks (12,13). O'Donnell and Kearon reported that discontinuation of anticoagulation within 1 month after acute VTE is associated with a recurrence rate of >40% (13). They also recommended preoperative inferior vena cava (IVC) filter insertion if delaying surgery is not feasible (13).

Hip fracture is a representative disease that requires early surgery to reduce mortality and perioperative complications (14,15). However, there are scarce data about the optimal timing of surgery and the clinical course in patients with hip fracture and acute PE. Thus, the current study aimed to evaluate the safety and clinical outcomes of early surgery within 1 month after acute PE in patients with hip fracture.

Methods

Study population and methods

We performed a retrospective cohort study at Asan Medical Center, a tertiary referral hospital in Seoul, South Korea. Patients with hip fracture diagnosed from January 2008 to December 2017 and who underwent surgery were screened. Among these patients, only those who were suspected to have PE and underwent pulmonary computed tomography (CT) angiography were included in this study. After excluding patients who were diagnosed with PE during the postoperative period, the included patients were classified into two groups: PE group, which included patients who had been diagnosed with PE before surgery, and the non-PE group, which included patients who had not been diagnosed with PE during the hospital stay. The diagnosis of PE and

DVT was confirmed with pulmonary CT angiography, lower-extremity venographic CT, and lower-extremity venous Doppler ultrasound. Initially, data on age, sex, body mass index, D-dimer level, history of malignancy, presence of DVT, and echocardiography findings were collected from the electronic medical records of Asan Medical Center. The severity of PE was evaluated using the simplified Pulmonary Embolism Severity Index (PESI) at the time of CT scan (16) and according to the 2014 European Society of Cardiology guidelines (17). The study protocol was approved by the institutional review board of Asan Medical Center (approval no. 2019-0394), and written informed consent was waived owing to the retrospective nature of the study.

Perioperative management

The perioperative management of patients with acute PE requiring surgery at our institution has been based on a review article by O'Donnell and Kearon (13) and the American College of Chest Physicians guidelines (18). In patients in whom surgery cannot be delayed for >3 months after the PE diagnosis, therapeutic dose bridging anticoagulation is recommended. In addition, in patients in whom surgery could not be delayed for >2 weeks after the PE diagnosis, preoperative IVC filter insertion is recommended. However, preoperative IVC filter insertion and postoperative anticoagulation were performed on a case-by-case basis according to the decision of the responsible surgeon.

Definition of outcomes

Adverse outcomes during 3 months after the surgery were evaluated. The primary outcomes in this study were symptomatic recurrent VTE and major bleeding. The secondary outcomes were clinically relevant nonmajor (CRNM) bleeding, amount of perioperative transfusion, length of hospital stay, and perioperative mortality. Major and CRNM bleeding were defined as in previous studies (19,20). Major bleeding was defined as fatal bleeding or surgical-site bleeding that requires a second intervention; overt bleeding with a hemoglobin decrease of ≥ 2 g/dL after the surgery or transfusion of ≥ 2 units of packed red blood cells; or intracranial, intraspinal, intraocular, retroperitoneal, and pericardial bleeding (21). CRNM bleeding was defined as overt bleeding that did not meet the criteria of major bleeding but needed medical attention, unscheduled visits to a medical institution, and discontinuation of anticoagulants,

Table 1 Baseline characteristics of patients

Variables	Total	PE group	Non-PE group	Postoperative PE group	P value*	P value**
No. of patients	156	90	50	16	–	–
Age, years	72.0±14.8	72.0±14.6	73.6±11.0	66.8±23.9	0.494	0.284
Male sex	41 (26.3)	26 (28.9)	12 (24.0)	3 (18.8)	0.533	0.476
Body mass index, kg/m ²	22.8±3.8	22.6±3.3	23.4±4.6	23.4±4.5	0.296	0.960
GFR <50 mL/min/1.73 m ²	18 (11.5)	11 (12.2)	5 (10.0)	2 (12.5)	0.692	0.545
Hemoglobin <10 g/dL	43 (27.6)	31 (34.4)	10 (20.0)	2 (12.5)	0.072	0.396
Platelet count <150,000/μL	32 (20.5)	17 (18.9)	12 (24.0)	3 (18.8)	0.475	0.476
Liver cirrhosis	2 (1.3)	2 (2.2)	0	0	0.538	NA
History of malignancy	25 (16.0)	17 (18.9)	7 (14.0)	1 (6.3)	0.462	0.372

Among the total patients, 16 were diagnosed with PE during the postoperative period. Data are presented as mean ± standard deviation or number (%), unless otherwise indicated. *, P value between PE and non-PE group, **, P value between non-PE and postoperative PE group. PE, pulmonary embolism; GFR, glomerular filtration rate, NA, not available.

or resulted in impairment of daily activities (22).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables were presented as number (percentage). Continuous variables were compared using the Mann-Whitney U-test, and categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. All P values were 2-tailed, with statistical significance set at P<0.05. All statistical analyses were performed using SPSS 20.0 (IBM Corporation, Armonk, NY, USA).

Results

Clinical characteristics of patients

A total of 156 patients with hip fracture and who underwent pulmonary CT angiography were identified, of whom 16 patients (10.3%) were diagnosed with PE during the postoperative period (postoperative PE group). Subsequently, 90 patients (57.7%) were classified into the PE group and 50 patients (32.1%) were classified into the non-PE group. The baseline characteristics of the patients in both groups are presented in *Table 1*. The mean patient age was 72 years, and 26.3% of the patients were men. There were no statistical differences in baseline

characteristics between the PE and non-PE groups, non-PE and postoperative PE groups.

In the PE group, DVT was identified in 38.9% of patients at the time of PE diagnosis (*Table 2*). In these patients, the most common classification of PE was PESI class II (45.6%), followed by PESI class III (31.1%) and PESI class I (15.6%). According to the European Society of Cardiology guidelines, all patients in the PE group were classified as having intermediate/low risk (38.9%) or low risk (61.1%). With respect to the involved artery level, the segmental pulmonary artery (47.8%) was the most frequently involved, followed by the lobar pulmonary artery (23.3%) and the subsegmental pulmonary artery (18.9%). Pulmonary infarction was observed in only 1 patient.

Perioperative management in PE group

The median duration between PE diagnosis and surgery was 2 days, and all patients in the PE group underwent surgery within 1 month after the PE diagnosis (*Table 3*). Half of the patients in the PE group underwent IVC filter insertion before surgery. In addition, 64.4% of the patients in the PE group received preoperative anticoagulation, with heparin (45.6%) as the most commonly used agent. The median operation time was 108 min, and the median time without anticoagulation after surgery was 40 h. About 95.6% of the patients in the PE group received postoperative anticoagulation, with low molecular weight

Table 2 Clinical characteristics and pulmonary CT angiography findings of the study patients with pulmonary embolism

Variables	Total (n=90)
DVT at the time of PE diagnosis	
Present	35 (38.9)
Absent	34 (37.8)
Unknown	21 (23.3)
PESI	
Class I	14 (15.6)
Class II	41 (45.6)
Class III	28 (31.1)
Class IV	6 (6.7)
Class V	1 (1.1)
Risk stratification*	
High risk	0
Intermediate/high risk	0
Intermediate/low risk	35 (38.9)
Low risk	55 (61.1)
Pulmonary CT angiography findings	
Single vessel involved	51 (56.7)
Multiple vessels involved	39 (43.3)
Artery involved	
Pulmonary trunk	0
Main pulmonary artery	9 (10.0)
Lobar pulmonary artery	21 (23.3)
Segmental pulmonary artery	43 (47.8)
Subsegmental pulmonary artery	17 (18.9)
Pulmonary infarction	1 (1.1)

Data are presented as number (%), unless otherwise indicated. *, risk stratification was performed according to the 2014 European Society of Cardiology guidelines. DVT, deep vein thrombosis; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; CT, computed tomography.

heparin (LMWH) (41.1%) as the most commonly used agent.

Clinical course comparison between groups

More patients in the PE group received postoperative

Table 3 Perioperative management of the study patients with pulmonary embolism

Variables	Total (n=90)
Median duration between PE diagnosis and surgery, days	2 [1–4]
Preoperative IVC filter insertion	45 (50.0)
Preoperative anticoagulation	
Heparin	41 (45.6)
LMWH	11 (12.2)
DOAC	6 (6.7)
Not performed	32 (35.6)
Duration of operation, min	108 [91–152]
Time without anticoagulation after surgery, hours	40 [18–71]
Initial postoperative anticoagulation	
Heparin	23 (25.6)
LMWH	37 (41.1)
DOAC	26 (28.9)
Not performed	4 (4.4)

Data are presented as number (%) or median [interquartile range], unless otherwise indicated. PE, pulmonary embolism; IVC, inferior vena cava; LMWH, low molecular weight heparin; DOAC, direct oral anticoagulant.

anticoagulation (treatment dose in the PE group, prophylactic dose in the non-PE group) than those in the non-PE group (95.6% vs. 54.0%, $P<0.001$) (Table 4). However, among the study patients, there were no symptomatic recurrent VTE and mortality cases within 3 months. Further, there were no statistically significant differences in major bleeding, CRNM bleeding, transfusion amount, bleeding site, and length of hospital stay between the two groups.

With vs. without IVC filter

Among the patients in the PE group, those who underwent IVC filter insertion had higher D-dimer levels (median 19.0 vs. 12.1 g/mL, $P=0.021$) than those who did not (Table 5). In addition, more patients in the IVC filter group had DVT at the time of PE diagnosis (57.8% vs. 20.0%, $P=0.001$) than those in the non-IVC filter group. However, there were no statistically significant differences in clinical outcomes such as bleeding and length of hospital stay between the IVC

Table 4 Comparison of clinical course between the PE and non-PE groups

Variables	Total	PE group	Non-PE group	P value
No. of patients	140	90	50	
Duration of operation, min	108 [93–140]	108 [91–152]	108 [96–136]	0.915
Postoperative anticoagulation*	113 (80.7)	86 (95.6)	27 (54.0)	<0.001
Time without anticoagulation after surgery, hours	40 [18–72]	40 [18–71]	40 [12–80]	0.779
Symptomatic recurrent VTE	0	0	0	N.A.
Perioperative mortality	0	0	0	N.A.
Bleeding				
Major bleeding	27 (19.3)	19 (21.1)	8 (16.0)	0.463
CRNM bleeding	16 (11.4)	12 (13.3)	4 (8.0)	0.342
Transfusion	43 (30.7)	31 (34.4)	12 (24.0)	0.199
Transfusion ≤2 units	29 (67.4)	21 (67.7)	8 (66.7)	
Transfusion >2 units	14 (32.6)	10 (32.3)	4 (33.3)	
Bleeding site				
Operation-site bleeding	40 (28.6)	28 (31.1)	12 (24.0)	0.372
GI tract bleeding	2 (1.4)	2 (2.2)	0	0.538
Urinary tract bleeding	1 (0.7)	1 (1.1)	0	>0.999
Length of hospital stay, days	14 [9–21]	13 [9–19]	16 [9–22]	0.362

Data are presented as mean ± standard deviation, median [interquartile range], or number (%), unless otherwise indicated. *, postoperative anticoagulation was administered as a treatment dose in the PE group and as a prophylactic dose in the non-PE group. PE, pulmonary embolism; VTE, venous thromboembolism; N.A., not available; CRNM, clinically relevant nonmajor; GI, gastrointestinal.

filter group and the non-IVC filter group.

Discussion

The current study investigated the safety and clinical feasibility of early orthopedic surgery within 1 month in patients with hip fracture and acute PE. Although 21.1% of patients in the PE group experienced major bleeding during 3 months after surgery, there was no difference in clinical course between the PE and non-PE groups. Our study suggests that early surgery is clinically feasible in patients with intermediate/low- or low-risk PE, when the perioperative management protocol based on the American College of Chest Physicians guidelines is properly applied.

Although previous studies focused on the incidence and prophylaxis of VTE after hip fracture surgery (10,23,24), several studies showed that preoperative VTE is also a common finding in patients with hip fracture (with an incidence ranging from 2.6% to 62%) (11,25–28). However,

there is no evidence about the timing of surgery in patients with hip fracture with preoperative VTE, especially in PE cases. Patients with VTE have a risk of recurrence, especially in the first 4 weeks (12). Thus, previous studies suggested that elective surgery should be delayed for at least 1 month from VTE diagnosis, as much as possible (13,29). However, previous studies did not consider the type of surgery, which might affect the clinical decision. Generally, hip fracture requires early surgery not only for improving function and mortality (15) but also for reducing complications (14). In addition, Cho *et al.* showed that patients who were admitted >72 h after injury had a higher prevalence of VTE than those who were admitted within 72 h after the injury (28), which emphasizes the importance of early surgery. Our current study revealed that a proper management strategy might reduce morbidity and mortality in patients with hip fracture and acute PE, especially in low-risk cases.

In the PE group in the current study, approximately

Table 5 Baseline characteristics and clinical outcomes according to IVC filter insertion in the PE group

Variables	IVC filter group	Non-IVC filter group	P value
No. of patients	45	45	
Age, years	71.6±15.6	72.4±13.8	0.791
Male sex	14 (31.1)	12 (26.7)	0.642
Body mass index, kg/m ²	22.7±3.2	22.4±3.4	0.659
D-dimer, g/mL	19.0 [8.1–30.2]	12.1 [4.4–22.5]	0.021
History of malignancy	7 (15.6)	10 (22.2)	0.419
DVT at the time of PE diagnosis			0.001
Present	26 (57.8)	9 (20.0)	
Absent	12 (26.7)	22 (48.9)	
Unknown	7 (15.6)	14 (31.1)	
Symptomatic recurrent VTE	0	0	NA
Perioperative mortality	0	0	NA
Bleeding			
Major bleeding	10 (22.2)	9 (20.0)	0.796
CRNM bleeding	9 (20.0)	3 (6.7)	0.063
Transfusion	19 (42.2)	12 (26.7)	0.120
Transfusion ≤2 units	15 (78.9)	6 (50.0)	
Transfusion >2 units	4 (21.1)	6 (50.0)	
Length of hospital stay, days	14 [9–21]	12 [9–17]	0.455

Data are presented as mean ± standard deviation, median [interquartile range], or number (%), unless otherwise indicated. IVC, inferior vena cava; DVT, deep vein thrombosis; VTE, venous thromboembolism; NA, not available; CRNM, clinically relevant nonmajor.

64.4% of patients received preoperative anticoagulation and nearly all patients (95.6%) received postoperative anticoagulation. Although major bleeding occurred in 21.1% of patients in the PE group, which is higher than the incidence reported in previous studies (ranging from 2% to 6%) (30,31), there was no significant difference compared with that in the non-PE group. To our knowledge, the timing of postoperative anticoagulation in patients with hip fracture and PE has never been established. The median

time without anticoagulation after surgery was 2 days in our study, which suggests that it is relatively safe to resume anticoagulation therapy in the early phase.

Interestingly, preoperative IVC filter insertion did not affect the clinical course in the PE group. Although the use of IVC filters has increased over time (32), the role of IVC filters is still controversial especially in patients with VTE with anticoagulation therapy (33,34). Moreover, potential adverse events might occur in patients with IVC filter insertion, including organ penetration, IVC thrombosis, device migration, and inability to retrieve the device (35,36). However, IVC filter insertion might be beneficial in patients with hip fracture and acute PE. In our current study, the IVC filter group had a higher incidence of DVT than the non-IVC filter group, which might be related to the responsible surgeon's assumption that patients with DVT will benefit the most from the procedure. Previously, in 122 patients who underwent preoperative IVC filter insertion, Kim *et al.* reported that captured thrombus was identified in 13.1% of patients during the postoperative period (37). However, further studies will be needed to determine the role of IVC filter insertion in patients with hip fracture and acute PE.

The current study has several limitations. First, our study was retrospective in nature, and pulmonary CT angiography and lower-extremity venographic CT were not performed in some patients. In addition, our study was performed at a single tertiary referral center. These study characteristics might have introduced selection bias. However, the study population was followed up for >3 months, which enabled us to investigate the safety outcomes in these patients. Second, as the type of perioperative anticoagulation was diverse in the PE group, it is difficult to perform meaningful comparisons of anticoagulation agents. Third, only 1 patient had right ventricular dysfunction and 1 patient was classified as having PESI class V in the PE group. Thus, further studies in patients with high-risk PE are needed in the future. Despite these limitations, our study is the first to investigate the safety of early surgery in patients with hip fracture and PE, especially low- and intermediate-risk PE.

In conclusion, early surgery in patients with hip fracture and acute PE might be relatively safe and clinically feasible. Further prospective studies with larger populations will be needed to confirm our results.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the institutional review board of Asan Medical Center (approval no. 2019-0394), and written informed consent was waived owing to the retrospective nature of the study.

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