Low-Molecular-Weight Heparin Use with Thrombolysis: Is it Effective and Safe? Ten Years' Clinical Experience

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Key Words

Low-molecular-weight heparin · Thrombolysis · Acute pulmonary embolism

Abstract

Background: There is no data on the use of subcutaneous low-molecular-weight heparin (SC LMWH) in cases that require thrombolysis. **Objective:** Having used SC LMWH with thrombolytics for more than 10 years, we aimed to review our data, share our experiences and find out whether the use of SC LMWH with thrombolytics had been effective and safe.

Method: This is a retrospective cohort study. Patients who were diagnosed as acute pulmonary embolism (PE) and received either SC LMWH treatment or SC LMWH with thrombolytics in our hospital (a tertiary hospital) between 2000 and 2010 were included in the study. For both treatments, the rates of mortality and complications were calculated. **Results:** A total of 392 patients, 210 female (53.5%) and 182 male (46.5%) with an average age of 60 years, ± 16 SD, with acute PE, were included in the study. Of these patients, 107 (27.2%) were massive and 285 (72.8%) were nonmassive and were administered SC LMWH plus thrombolytics and only SC LMWH, respectively. The mortality rate was 16.8% (18 of 107) in patients who were massive and 3.5% (10 of 285) for those who were nonmassive ($p < 0.001$). Major hemorrhage oc-

curred in 3.7% ($n = 4$) and 0.7% ($n = 2$) and minor hemorrhage in 12.1% ($n = 13$) and in 3.8% ($n = 11$) of the cases who received SC LMWH plus thrombolytics and SC LMWH, respectively. **Conclusion:** SC LMWH use with thrombolytics seems to be feasible and safe. Prospective, large, randomized control trials are still required in order to confirm these results.

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Introduction

Acute pulmonary embolism (PE) is a common and often fatal disease, with an approximately 30% mortality rate without treatment [1]. Anticoagulation is the mainstay of the therapy for acute PE. It decreases the mortality rate to 3–8%, when effective therapy is instituted as quickly as possible [2, 3]. In acute PE cases, therapeutic options include subcutaneous low-molecular-weight heparin (SC LMWH), intravenous unfractionated heparin (IV UFH), subcutaneous unfractionated heparin and subcutaneous fondaparinux with or without thrombolysis [3].

In the treatment of acute PE, SC LMWH is at least as effective and safe as IV UFH [4]. Compared to IV UFH, SC LMWH results in lower mortality, fewer recurrent

thrombotic events and less major bleeding [5]; however, current guidelines recommend the use of SC LMWH for most hemodynamically stable patients with PE and that SC LMWH has not been tested in the setting of hypotension and shock [3, 6]. However, we have been using SC LMWHs in the cases with acute PE with or without the requirement of thrombolysis in our clinical practice since they have been available, because of their advantages for practical use and their use in primary or secondary care upon suspicion of PE just before their admission to our hospital.

Having used SC LMWH for at least 10 years in our clinic, a tertiary hospital, for cases requiring thrombolysis, we aimed to review our data, share our experiences and find out whether SC LMWH use with thrombolytics was indeed effective and safe in those cases.

Methods

Study Population

Patients who were diagnosed as having acute PE and who received either SC LMWH or SC LMWH plus thrombolytic treatment in our hospital (a tertiary hospital) between 2000 and 2010 were included in the study. The study population included all patients in each category (massive, submassive and low-risk) of PE. We excluded patients with any contraindication to the use of SC LMWH, such as active bleeding, during their admission.

Study Design

This was a retrospective cohort study. Data collection was done by medical record review using an existing clinical database. All demographic, clinical and laboratory findings as well as treatment choices and their outcomes were recorded. The local ethical committee at the Faculty of Medicine, Ataturk University, approved the protocol of the study (IRB B.30.2.ATA.0.01.00/13).

Diagnostic Work-Up

All patients with clinical suspicion of PE (major risk factors and clinical manifestations) underwent chest X-ray, electrocardiogram (ECG), echocardiographic evaluation and either a helical (in the first 3 years) or a 16-slice multidetector computerized thorax (CT) angiography (if there was no contraindication) or a ventilation/perfusion (V/Q) lung scan. Ultrasonographic examinations were performed with the Aplio US system (Toshiba, Tokyo, Japan), a high-resolution 7.5-MHz wideband transducer used by an experienced radiologist. The patient has to briefly lie in the supine position in a dark room. The common femoral vein, superficial femoral vein, saphenofemoral junction, popliteal vein, saphenopopliteal junction and posterior tibial vein were studied with duplex ultrasonographic scanning. Sonographic examinations were evaluated for the cardinal features that are accepted as diagnostic of lower extremity DVT noncompressibility of the affected deep vein(s), nonvisualization of deep vein(s) on color Doppler imaging, or both [7].

Pharmacological Regimen

Fixed-dose SC LMWH (enoxaparin or nadroparin) was applied for the treatment of acute PE at the initial hospital admission. According to clinical category, thrombolytic treatment was initiated within 14 days after onset of symptoms to those patients requiring it. We used alteplase (10 mg bolus alteplase followed by 90 mg over 2-hour infusion) or streptokinase (250,000 units bolus streptokinase applied over half an hour, followed by 1,250,000 units over 24–72 h) as a fibrinolytic. After fibrinolytic therapy (FT), 4–6 h later, activated partial thromboplastin time was checked. According to initial SC LMWH use time, fixed-dose SC LMWH (enoxaparin or nadroparin) was administered subcutaneously every 12 h, and overlapped with warfarin on days 1–5 or the day on which the targeted international normalized ratio level was achieved. The patients were kept on warfarin, aiming for an international normalized ratio of between 2.0 and 3.0 for 3 months or more, depending on the presence of major risk factors.

Definitions

Massive PE is defined as acute PE with sustained hypotension (systolic arterial pressure <90 mm Hg or a drop in systolic arterial pressure of at least 40 mm Hg for at least 15 min) and cardiogenic shock (including an altered level of consciousness, oliguria or cool, clammy extremities) [8].

Submassive PE is defined as acute PE without systemic hypotension (systolic blood pressure $\geq$ 90 mm Hg) but with either right ventricular (RV) dysfunction (i.e. the presence of at least 1 of the following: RV dilation or RV systolic dysfunction on echocardiography, RV dilation on CT, elevation of BNP, elevation of N-terminal pro-BNP or electrocardiographic changes) or myocardial necrosis [either of the following: elevation of troponin I (>0.4 ng/ml) or elevation of troponin T (>0.1 ng/ml)] [8].

Low risk PE is defined as the patients who are normotensive with no RV dysfunction on echocardiography [8].

Major hemorrhage is defined as stroke (confirmed by computed tomography), hematoma >5 cm, oral or gastrointestinal bleeding or other bleeding with concomitant hypotension requiring treatment with intravenous fluids, blood transfusion, surgical control, discontinuation of the FT regimen, decrease >15% points in hematocrit or a reduction in hemoglobin of >5 g/dl [9].

Minor hemorrhage is defined as a decrease of between 10–15% points in hematocrit or a reduction in hemoglobin of 3–5 g/dl [9].

Recurrent PE is defined as clinical suspicion of new PE symptoms, new signs on in-hospital ECG with or without clinical instability or death.

Statistical Analysis

Statistical analysis was performed with SPSS for Windows version 17.0 (SPSS Inc., Chicago, Ill., USA). Data were expressed in percent, mean and standard deviation, odds ratio and 95% confidence interval. We used the two-tailed Student t test for comparisons of continuous variables between patients with massive and nonmassive PE and the Pearson χ^2 test or the Fisher Exact test for comparisons of nominal variables. We performed an analysis adjusting for confounders using logistic regression. One-year and 5-year survival estimations were done by means of the Kaplan-Meier survival probability estimates. Patients who died during the in-hospital phase were excluded from the 1-year and 5-year survival analyses. Findings were considered statistically significant if a p value of <0.05 was obtained.

Results

From 2000 to 2010, a total of 392 patients, 210 female (53.5%) and 182 male (46.5%) with an average age of 60 years $\pm$ 16 SD with acute PE were included in the study. Of these, 107 (27.2%) had massive PE and 285 (72.8%) had nonmassive PE and they were administered with SC LMWH plus FT and SC LMWH, respectively. Patient characteristics are shown in table 1. In both treatment groups, the ages and clinical features were different, but there were more women than men and DVT was the most common concomitant disorder. The other risk factors determined in the study are also shown in table 1. Hospital stay was longer for massive PE patients than for nonmassive PE patients (12 ± 6 vs. 10 ± 5 days) ($p < 0.001$).

The diagnosis of PE was definite with positive CT angiography ($n = 380$) or V/Q lung scan ($n = 12$).

Mortality rate, duration of hospitalization and bleeding complications are presented in table 2. The all-cause mortality rate was 7.1% (28 deaths) during the first 2 weeks after the diagnosis. The mortality rate was 16.8% (18 of 107) in patients who were hemodynamically unstable at the time of presentation and 3.5% (10 of 285) for those who were hemodynamically stable ($p < 0.001$). Twenty deaths (5.1%) were attributed to recurrent PE, 7 (6.5%) to thrombolytic complications (including massive hemoptysis and shock) and 1 (0.2%) was due to respiratory failure.

The probability of 1-year and 5-year survival was 87 and 85% in the massive PE group and 93 and 90% in the nonmassive PE group, respectively.

Major hemorrhage occurred in 3.7% ($n = 4$) of the cases who received SC LMWH plus FT, all of which were massive hemoptysis cases as well as in 0.7% ($n = 2$) of the cases who received SC LMWH only (1 intramuscular and 1 intraperitoneal hemorrhage that needed a blood transfusion), but this difference was not statistically significant ($p = 0.05$).

Minor hemorrhage occurred in 12.1% ($n = 13$) of the cases who received SC LMWH plus FT and in 3.8% ($n = 11$) of those who received SC LMWH only. The difference was statistically different ($p = 0.004$). There was a relationship between minor hemorrhage and immobilization.

Logistic regression analysis showed that some confounding factors were associated with increased mortality and bleeding complications including chronic obstructive pulmonary disease (COPD), immobilization (bedrest for 5 days or longer) and obesity (which can also be related immobilization) (table 3). COPD and obesity were associated with an increased risk of death ($p = 0.001$ and $p = 0.04$, respectively). Immobilization was associ-

Table 1. Patient characteristics ($n = 392$)

	Massive PE ($n = 107$)	Nonmassive PE ($n = 285$)	p
Age, years	63 ± 15	59 ± 16	0.03
>65 years	60 (56)	113 (39.6)	0.004
Male	45 (42)	137 (48)	0.3
Female	62 (58)	148 (52)	
Systolic pressure, mm Hg	93 ± 17	114 ± 14	<0.001
Dyastolic pressure, mm Hg	57 ± 10	70 ± 8	<0.001
Dyspnea	98	245	0.17
Chest pain	73	189	0.8
Syncope	42	36	<0.001
Substernal pain	27	38	0.006
Palpitation	53	72	<0.001
Previous or concomitant diseases			
Chronic obstructive lung disease	10 (9.3)	21 (7.3)	0.5
Cancer	7 (6.5)	18 (6.3)	1
DVT	48 (45)	82 (29)	0.004
Immobilization	59 (55)	152 (53)	0.8
Biomass	41 (38.3)	63 (22)	0.002
Smoking	20 (18.6)	104 (36.4)	0.001
Diabetes mellitus	12 (11.2)	30 (10.5)	0.85
Hypertension	32 (30)	82 (29)	0.9
Congestive heart failure	5 (4.6)	17 (6)	0.8
RV hypokinesis	22	11	<0.001
Right heart thrombus	5	0	<0.001
Pulmonary arterial pressure, mm Hg	60 ± 15	34 ± 24	<0.001

Data are expressed as mean $\pm$ SD or number with percentage in parentheses.

Table 2. In-hospital outcome and adverse events

	Massive PE	Nonmassive PE	p
Mortality	18	10	<0.001
Related thrombolysis	7	–	
Recurrence of PE	10	10	0.02
Acute respiratory failure	1	–	
In-hospital stay, days	12 ± 6	10 ± 5	<0.001
Major hemorrhage	4	2	0.05
Minor hemorrhage	13	11	0.004

ated with an increased risk of minor hemorrhage ($p = 0.001$). After excluding the patients who died during hospitalization, logistic regression analysis showed that both COPD and cancer have a significant effect on mortality ($p < 0.001$).

Table 3. Baseline characteristics and in-hospital adverse events

	Mortality p (95% CI)	Major hemorrhage p (95% CI)	Minor hemorrhage p (95% CI)
Age	0.21 (0.95–1)	0.24 (0.84–1)	0.8 (0.9–1)
COPD	<0.001 (0.02–0.25)	0.53 (0.05–4.7)	0.9 (0.1–1)
Diabetes mellitus	0.9 (0.2–2.5)	0.9 (0.1–1)	0.07 (0.1–1.1)
Massive PE	0.2 (0.08–1.7)	0.58 (0.2–2.4)	0.06 (0.03–1.1)
Nonmassive PE	0.1 (0.02–1.4)	0.99 (0.1–1)	0.19 (0.02–2.09)
Thrombolytic treatment	0.4 (0.1–2.6)	0.23 (0.2–2.4)	0.75 (0.2–7.2)
Immobilization	0.5 (0.3–1.8)	0.09 (0.7–5)	0.01 (1.2–7.8)
Smoking	0.07 (0.8–12)	0.9 (0.1–1)	0.7 (0.2–2.3)
Biomass	0.1 (0.1–1)	0.8 (0.1–6.5)	0.8 (0.2–2.7)
Obesity	0.04 (0.08–1)	0.9 (0.1–1)	0.9 (0.2–4.7)

Discussion

Our study suggests that there was no unacceptable increase of treatment-related complications, such as hemorrhage, recurrence or death, with the use of SC LMWH with FT, compared to the use of SC LMWH alone, although the severity of the diseases are not completely comparable.

This study does not provide a head-to-head comparison of the use of SC LMWH and IV UFH in the cases with massive PE, but its results suggest that the use of SC LMWH may be an option in the treatment of these cases. There are no data and/or recommendations on the use of SC LMWH along with FT in the cases of PE who require thrombolytics, but SC LMWH is widely used in cases not requiring thrombolysis. This is due to its practical use, greater bioavailability, fixed dosing that does not require adjustment and the decreased likelihood of thrombocytopenia [3]. Compared to IV UFH, SC LMWH use in cases not requiring thrombolysis results in lower mortality and fewer recurrent thrombotic events [5].

In our clinical practice as a tertiary center, the patients with PE commonly apply to our hospital after administration of SC LMWH as part of their prior application to the primary or secondary care with clinical suspicion of PE or administration of SC LMWH in our emergency department before consultation in the pulmonary disease department. The main reason to use SC LMWH in cases of massive PE is to avoid increased complications (especially hemorrhagic ones). However, their half-life is longer and mostly we apply thrombolytic treatment without waiting for the end of their half-life. Due to barely encountering any serious complications in such cases, we started to use SC LMWH instead of IV UFH, not only in

cases requiring anticoagulation alone but also in cases requiring thrombolytics.

Intravenous unfractionated heparin was once the preferred initial treatment for acute PE because it was the only anticoagulant that had been compared to no treatment in a controlled trial and was shown to reduce mortality due to PE [10]. The main advantages of using it are: a short half-life, hepatic clearance, effective antidote and an available test to determine its activity. However, individual trials suggest SC LMWH to be the preferred anticoagulant for initial therapy in most cases of acute PE [5]. In addition, monitoring anti-Xa levels is not necessary for most patients receiving LMWH except those with morbid obesity, low body weight, renal insufficiency or who are pregnant. The therapy of IV UFH requires monitoring on activated partial thromboplastin time, so patients with acute PE need hospitalization. The efficacy of IV UFH also depends upon achieving a therapeutic level of heparin within the first 24 h of treatment [11]; because achieving this sometimes fails, inadequate initial heparin therapy may increase the probability of recurrent PE for at least 3 months despite ongoing therapeutic anticoagulation [12].

Individual studies and meta-analyses of trials have reported that SC LMWH is at least as effective and safe as IV UFH with no increase in major bleeding events, in the treatment of acute PE [4]. In our study, major bleeding was 3.7% (including massive hemoptysis) and the difference between receiving SC LMWH alone and SC LMWH plus thrombolytics was not statistically significant. When we did a search on the studies, using IV UFH with thrombolytics, we determined that our results are comparable and even better than many of them [13–16]. For example, ICOPER (International Cooperative Pulmonary Embo-

lism Registry) reported that major bleeding was 21.7% in patients who received thrombolytic therapy [13] and in the other studies, the frequency of major bleeding in the cases who receiving IV UFH plus thrombolytics varies between 2 and 28% [13–16].

PE, especially massive PE, continues to have a high mortality rate. This rate varies between 30 and 62% in patients with PE who are hemodynamically unstable at presentation [13, 17, 18]. In our study, PE was the cause of death in 16.8% of the patients with massive PE at day 14. These deaths were most probably due to recurrent PE. The rate of recurrent PE was 9.3% in the SC LMWH plus thrombolytics group versus 3.5% in the SC LMWH group. This difference was statistically significant. However, it might be related to the clinical severity of the SC LMWH plus thrombolytics group, a longer period of immobilization or concomitant disorders [19]. The ICOPER reported that the mortality rate due to recurrence was 33.7% at day 14 and recurrent PE was detected within 90 days in 12.6 and 7.6%, respectively, in patients with massive versus nonmassive PE [13]. Konstantinides et al. [20] reported that they had a 3.4% in-hospital recurrence rate, but this study included acute PE patients who were hemodynamically stable. Recent meta-analyses, comparing thrombolysis with IV UFH, reported that the recurrent PE rate ranged from 4.9 to 9.4% [15, 17]. When we did a logistic regression analysis for confounders, it showed that COPD and obesity were associated with an increased risk of death ($p = 0.001$ and $p = 0.04$, respectively). This data may show that a concomitant disorder is important in the course of PE and also for recurrence. In addition, the long-term analysis showed that concomitant disorders, especially COPD and cancer ($p = 0.001$), are important for 1-year and 5-year survival.

Previous meta-analysis comparing thrombolysis with IV UFH has demonstrated that thrombolysis has an increased risk for minor bleeding (it may reach 22%) compared to heparin (10%) [16]. In our study, minor bleeding occurred in 12.1% of the cases who received SC LMWH

plus thrombolytics and in 3.8% of the cases who received SC LMWH alone. This showed minor bleeding to be within an acceptable range. In addition, when we did logistic regression analysis for confounders, we found that immobilization was associated with an increased risk of minor bleeding ($p = 0.001$). Because of the clinical severity of the thrombolytic group, the period of immobilization might have been longer and have affected the rate of minor bleeding; this may show that early mobilization could be important to decrease the rate of minor hemorrhage.

The limitation of our study was that the data reported herein are not from a prospective, randomized, controlled trial (RCT) – including the cases who were administered IV UFH plus thrombolytics in comparison to the cases who were administered SC LMWH plus thrombolytics. The study did not make a head-to-head comparison, so it is reasonable to expect that the results of the massive PE group, including their blood pressure and age, would be worse than those of the other group. Although the patients in the massive PE group were older, the mortality rate over the first year following PE was 13% and mortality was associated with underlying diseases but not with age. In the literature, mortality rate varies between 17 and 24% [21–23]. However, this is a real-life study and it may be a base for future RCTs.

As a conclusion, the use of SC LMWH with thrombolytics (and even in the cases in our study where only SC LMWH was used) when compared to the studies in the literature (using IV UFH with thrombolytics) is feasible and safe. However, prospective, larger RCTs are required in order to confirm these results.

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