Incidence and Characteristics of Pulmonary Thromboembolism in Japan 2000

Osamu KITAMUKAI, Masahito SAKUMA, Tohru TAKAHASHI, Yutaka KAGAYA, Jun WATANABE and Kunio SHIRATO

Abstract

Objective The incidence of pulmonary thromboembolism (PTE) is much lower in Japan than in the United States. The number of deaths from PTE, however, has gradually increased. The present study was designed to investigate the incidence and characteristics of PTE in Japan.

Methods and Materials We sent 5,582 questionnaires to inquire about the number of new cases of PTE between August 1, 2000 and September 30, 2000. We received 1,702 replies and 205 new cases were registered. The number of new cases per year was 4,022 (95% confidence interval: 3,704–4,305) and the incidence was 32 (95% confidence interval: 29.2–33.9) patients per 1,000,000 people per year. Main risk factors were immobilization, surgery, trauma, and malignancy. The mortality within a month and 6 months was 16% and 20%, respectively. Half of the deaths within a month occurred on the diagnosis day.

Conclusion The results showed that the incidence of PTE in Japan 2000 tended to increase compared with that in 1996, but it was still much lower than that in the United States.

Introduction

We previously reported that the incidence of pulmonary thromboembolism (PTE) in Japan is very low in comparison to that in the United States (1, 2). The vital statistics in Japan, however, revealed that the number of deaths with PTE has gradually increased (3). Furthermore, a fatal PTE often occurs in hospitalized patients. Therefore, the burden of PTE is increasing in Japan. The purpose of this study was to investigate whether or not the incidence of clinically diagnosed PTE is increasing and to assess the characteristics of PTE in Japan.

Methods

In July 2000, we sent questionnaires to assess prospectively the number of newly diagnosed patients with PTE between August 1, 2000 and September 30, 2000 to the clinical departments (all departments of internal medicine, all departments of surgery, pediatrics, psychiatry, obstetrics and gynecology, orthopedics, otolaryngology, ophthalmology, dermatology and urology) of university schools of medicine or medical colleges and to hospitals with more than 100 beds in Japan. Again in August 2001, we sent the questionnaires to the institutes, which had had newly registered cases during the period, and examined the late mortality of these cases and their characteristics in detail. PTE was definitely diagnosed by 1) pulmonary angiography, 2) pulmonary perfusion scintigraphy and/or pulmonary ventilation scintigraphy, 3) enhanced CT, 4) MRI, or 5) autopsy. From the number of newly diagnosed patients with PTE in 2 months, the number of mean cases in a hospital or a clinical department and the 95% confidence interval of the mean were estimated. Then, the number of patients with PTE per year was calculated as follows: the number of patients with PTE per year=the number of patients with PTE per 2 months×6/the response rate. The mortality within a month of patients treated with anticoagulation alone and that of those treated with thrombolysis with or without anticoagulation were compared by chi-square analysis.
Incidence and Characteristics of PTE in Japan

Table 1. Questionnaires

<table>
<thead>
<tr>
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<th>Sent letters</th>
<th>Reply</th>
<th>With cases</th>
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<tbody>
<tr>
<td>University</td>
<td>1,906</td>
<td>767 (40.2%)</td>
<td>50 (6.5%)</td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>548</td>
<td>180 (32.8%)</td>
<td>27 (15.0%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>588</td>
<td>274 (46.6%)</td>
<td>11 (4.0%)</td>
</tr>
<tr>
<td>Others</td>
<td>770</td>
<td>313 (40.6%)</td>
<td>12 (3.8%)</td>
</tr>
<tr>
<td>Hospital</td>
<td>3,659</td>
<td>935 (25.6%)</td>
<td>108 (11.6%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5,565</strong></td>
<td><strong>1,702 (30.6%)</strong></td>
<td><strong>158 (9.3%)</strong></td>
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Number of closed institutes was excluded from the number of sent letters. Numbers in parentheses are response rate and rate of institutes with pulmonary thromboembolism patients. “Surgery” includes all departments of surgery, obstetrics and gynecology, and orthopedics. “Others” indicates all departments other than internal medicine and surgery.

Results

A total of 5,582 letters were sent to the above-mentioned departments and hospitals. Seventeen institutes were excluded from our analysis because the institutes had closed. We received 1,702 replies to the initial letters (see Table 1). The response rate was 30.6%. The number of newly diagnosed patients with PTE was 205 during the 2 months of the present study period (88 men and 117 women; mean age 62.0±16.9 [SD] years old). The age and sex distribution is shown in Fig. 1. The number of patients in their sixties was the highest in both men and women. In the patients under forty, the number of men was greater than that of women. In the patients forty or older, the number of women was greater than that of men.

The estimated number of newly diagnosed patients with PTE per year was 4,022 (95% confidence interval: 3,704-4,305) and the incidence of PTE was 32 (95% confidence interval: 29.2–33.9) patients per 1,000,000 people per year in Japan. Acute PTE represented 86% of all cases. The major risk factors were immobilization, surgery, trauma, and malignancy (Table 2). Eleven percent of the patients did not have any risk factor.

The treatment within a month from the diagnosis of PTE is shown in Table 3. The most common treatment was anticoagulation by heparin and/or warfarin. Thrombolysis was performed in 34% of the patients with urokinase and in 15% of the patients with tissue plasminogen activator. Invasive and aggressive treatments such as catheter intervention, percutaneous cardiopulmonary support, and surgical thromboembolectomy were performed in a small number of patients. The maximum daily dose and the administered period of heparin and urokinase are shown in Figs. 2 and 3, respectively.

The Kaplan-Meier survival curve is shown in Fig. 4. The mortality within a month and 6 months from diagnosis was 16% and 20%, respectively. Half of the deaths within a month occurred on the day that PTE was diagnosed. Eight patients were treated with either catheter intervention, percutaneous cardiopulmonary support, or surgical thromboembolectomy, or a combination, however 4 (50%) of these 8 patients died within a month. Fifteen percent of the patients treated with anticoagulant alone and 13% of the patients...
Table 3. Treatment of PTE within a Month from Diagnosis

<table>
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<tr>
<td>Heparin</td>
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<tr>
<td>LMW-heparin</td>
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<td>Warfarin</td>
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<td>Antiplatelets</td>
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<td>Urokinase</td>
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<td>t-PA</td>
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<td>IVC filter</td>
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<td>Catheter intervention</td>
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<td>PCPS</td>
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<td>Thromboembolectomy</td>
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Discussion

The estimated number of new patients with PTE per year was 4,022 and the incidence of PTE was 32 (95% confidence interval: 29.2–33.9) patients per 1,000,000 people per year in 2000. Compared with our previous report (1) that estimated the incidence of PTE in 1996 (28 patients [95% confidence interval: 26.1–29.4] per 1,000,000 people per year), the incidence of PTE in Japan showed a tendency to increase. Some reasons for the increase in the incidence are thought to be due to an increment of the risk factors for DVT and PTE such as malignancy and obesity and because an elder population has a higher risk for PTE (4–6). These reasons, however, do not seem to offer a sufficient explanation for the increased incidence in only 4 years. Improvements in medical instruments, for example the appearance of helical CT (7) and the increased concern for PTE among physicians, are considered as other reasons. It is difficult to assess the increased concern for PTE objectively, but it is true that traveler’s thrombosis, so-called “economy class syndrome”, has become widely recognized. A previous study in the United States (8) reported that the prevalence of concern for PTE played a part in the increased mortality of PTE from 1962 to 1974. Some investigators mentioned that there may be seasonal variation in the occurrence of PTE (9, 10), and if so, the present estimation of the incidence of PTE would be affected. But our preliminary data showed no such variation in Japan (11). Therefore, we did not take into consideration the seasonal change when calculating the incidence.
It has been estimated that the number of patients with PTE per year in the United States is 630,000 (12). In that paper, the incidence was estimated using reported data in the literature, and cases with PTE were not directly examined. Although the incidence of PTE in Japan has increased during the past four years, it is still very low compared with that in the US.

As shown in our previous report (1), there were some potential differences for the difference in the incidence between Japan and Western countries, such as differences in the levels of serum lipid (13, 14), the frequency of factor V Leiden mutations (15-17), and the accuracy in the diagnosis of PTE (18).

Recent reports suggested that not only factor V Leiden mutations but also prothrombin G20210A mutations increased the risk for DVT and PTE, and that these were rare in Southeast Asia compared with Western countries (15, 19, 20). Moreover, these mutations have not been found yet in Japan (16, 17). The mortality for PTE in non-black and non-white populations was lower than that in both black and white populations in the United States (21), suggesting that there are some racial differences that influence the incidence of PTE.

The present study showed that thrombolysis was performed in 34% of the patients using urokinase and in 15% of the patients using tissue plasminogen activator. There was no significant difference in the mortality within a month from the diagnosis of PTE between the patients administered anti-coagulation alone and those who underwent thrombolysis with or without anticoagulation. It is disputable whether thrombolysis improves the prognosis of PTE. Although there is a report that thrombolysis decreased the mortality in cases with unstable hemodynamics (22), the mortality in patients with stable hemodynamics and right ventricular dysfunction was not improved by thrombolysis (23). The international consensus recommendation by ECC and ACCP (24) described that thrombolysis requires further clinical study for common use. Thus, there is a need for randomized clinical trials to determine the appropriate use of thrombolysis and its effect on mortality.

The administered dose and period of heparin and urokinase were varied in Japan, likely because of differences in the coexistent disease and the severity of PTE in each case. An additional reason may be because there are no guidelines for the management of PTE in Japan yet.

The mortality within a month and 6 months from the diagnosis was 16% and 20%, respectively and most of the deaths were within one month from diagnosis, with one-half of these cases dying within one day. This suggests that early treatment could greatly decrease the mortality of PTE. In the patients of the present study, invasive and aggressive treatments such as catheter intervention, percutaneous cardiopulmonary support, and surgical thromboembolectomy were performed in only 6% of the patients. In spite of such treatment, 50% of these died within a month. Thus, the main problem is to decrease the mortality for severe cases in the early period after diagnosis.

In conclusion, the present study showed that the incidence of PTE in Japan in 2000 tended to increase compared with that in 1996, but the incidence was still much lower than that in the United States. Because most of the deaths were within a month after diagnosis, in order to decrease the mortality there is a need for a more effective diagnosis and treatment in the early period.

Acknowledgement: We thank all of the institutions that replied to our questionnaires.

References


