Results of the PHLEFI Study (PHLEbothrombosis-Fibrinolytic Therapy): A Prospective, Multicenter Study of the Fate of 1498 Patients Receiving Fibrinolytic Therapy for Deep Vein Thrombosis

M. Martin, M.D.

PHLEFI Coordination Center, Geriatrische Klinik, Duisburg, Germany

Abstract. Fibrinolytic therapy for DVT has not gained universal acceptance. A notable percentage of DVTs in Germany are treated by clot-dissolving methods. This is in contrast to clinical practice in the United States where fibrinolytic treatment for DVT is virtually unknown. It is unique in modern medicine that such a frequent disease is treated so differently on a national basis. The PHLEFI Study is a multicenter, prospective trial on the fate of 1498 patients receiving different forms of fibrinolytic therapy for DVT (ultrahigh streptokinase and urokinase short-term therapy, streptokinase, urokinase, and rt-PA long-term infusions, locoregional and sequential therapies). Interest focused primarily on side-effects such as cerebral bleeding and fatal pulmonary embolism as well as on the clinical outcome in terms of revascularization. The major factor for the rate of cerebral bleeding under fibrinolytic therapy was the age of the patient (0.355% bleeding in patients under and 2.03% in patients over 50 years). The major factor for pulmonary embolism was the site of the thrombosis (2.16% with iliac, 0.701% with femoral, none with popliteal, calf and subclavian vein thromboses). Use of a temporary caval filter during lysis therapy eliminated fatal pulmonary embolism. Results of lytic therapy were stated as complete, partial, and no clearance. The outcome was dependent on the thrombus age and the medication used. The highest clearance rate achieved was 50% in patients treated with short-term ultrahigh streptokinase therapy and a history of up to three days. Fibrinolytic therapy for DVT is a reliable means of achieving revascularization. The above data may enable the physician to balance the usefulness of this therapeutic method against the risk of its side effects.

Methods

Design

The study record forms consisted of two A4 pages with two carbon copies. Part I of the form (Data at entry) contained the date of admission of a patient with DVT, together with details of the patient’s age, thrombosis location and duration, and information on whether phlebography had been performed or not. This initial notification was forwarded to the Coordinating Center within 10 days after admission. Part II of the form (Further data and clinical course) opened with questions concerning the cause of thrombosis and the type of treatment given. If the answer to the second of these questions was “conservative (heparin) therapy” or “surgery,” the case report was closed. However, if the answer was “fibrinolytic therapy,” the study continued by eliciting the following information: details of fibrinolytic medication, site of infusion (leg, arm), dosage regimen (including concomitant heparin and coumarin treatment), phlebographic control, result of lysis (complete, partial, no clearance), as well as fatal or non-fatal complications (cerebral and non-cerebral bleeding, severe organ bleeding, pulmonary embolism). This copy was forwarded to the Coordinating Centre within 10 days following discharge or death. The second carbon copy was retained by the hospital for its own records.

No predefined procedure was laid down. It was assumed that each centre would perform diagnosis and treatment procedures in line with routine clinical practice. The only requirement was that the relevant data agreed on at the beginning of the study should be forwarded to the Coordinating Centre.

Hospital Participation

A total of 47 medical departments participated in the study. The average number of beds per department was 103 ± 31.4 (range: 40–164). Seventeen (36.2%) of the hospitals involved were affiliated to religious denominations, 21 (44.7%) were run by local (municipal or district) authorities, 5 (10.6%) were charitable foundations, 3 (6.3%) were university hospitals, and 1 (2.1%) was run by the Red Cross.

Results

Frequency of Notification

Within the 4-year period covered by the study, an average of 56.6 ± 75.1 record forms per centre were returned (range: 1–320). Of the centres participating, 51.1% mailed up to 24 record forms, 12.8% mailed 25–49 record forms, 10.6%
mailed 50–74 record forms, 8.51% mailed 75–100 record forms, and 17.0% mailed more than 100 record forms. During the period between 1st January 1992 and 1st January 1996 a total of 2656 patients with DVT were entered in the study. This translates into 0.562 patients with DVT per bed over a period of 4 years. Thus, an average department with 103 beds admitted one patient with DVT every 3.58 weeks.

**Definition and Characteristics of Patient Groups**

A total of 2656 patients were registered (Group A). This number consisted of 1141 patients (43.0%) receiving conservative therapy, 17 patients (0.640%) who were treated by surgery, and 1498 patients (56.4%) receiving fibrinolytic therapy (Group C). The phlebography rate prior to treatment was 91.5% for the total study population, 85.6% for those receiving conservative therapy, 88.2% for those treated by surgery, and 96.0% for those receiving fibrinolytic therapy (Group C). Group D encompassed patients who were treated by fibrinolytic therapy and investigated by phlebography prior to treatment. In 31 patients fibrinolytic therapy was performed under the protection of a removable caval filter, thus leaving 1407 patients in Group D1. Group E comprised 1324 patients who received fibrinolytic therapy and underwent phlebography before and after therapy.

Table 1 defines Groups A to E with their background characteristics.

The patients’ age and gender ratios varied with the thrombosis site. Patients with subclavian vein thromboses were approximately 10 years younger than patients with leg vein thromboses. In addition, women presenting with ili and calf vein thromboses outnumbered men and men with subclavian vein thrombosis outnumbered women, whereas the gender ratios for the remaining occlusion sites were evenly balanced (Table 2).

The length of hospital stay was 19.8 ± 12.0 days for Group C (patients receiving fibrinolytic therapy) and 19.5 ± 11.1 days for Group D (patients receiving fibrinolytic therapy with phlebography before and after fibrinolytic therapy).

**Assumed Causes of Thrombosis (Group B)**

Immobility was the principal factor responsible for the development of thrombosis. Other causes listed included surgery, hormone therapy, tumor, trauma, and blood coagulation abnormalities. The rate of unknown causes was high, accounting for nearly one-third of cases. The frequency of coagulation defects was relatively low (0.905%) when compared with data from the literature [2]. However, it should be borne in mind that far from indicating an insignificant role of coagulation factors for thrombotic disorders, this relatively low rate of <1% rather shows that coagulation tests were carried out in only a limited number of cases.

**Thrombosis Duration (Group B)**

At the time of admission to hospital the thrombotic event dated back 7.11 ± 7.84 days on average. Patients with subclavian vein thrombosis were admitted earliest (5.60 ± 5.83 days after the initial symptoms), followed by patients with thrombosis of the calf veins (6.50 ± 7.34 days), popliteal veins (6.62 ± 6.18 days), ili veins (6.82 ± 8.70 days), and femoral veins (7.59 ± 8.06 days).

**Thrombosis Location (Group B and D)**

Group B (unselected patients who had undergone phlebography at entry) comprised 2430 patients, and only the most proximal location was recorded for each patient. Since 38 patients presented with bilateral occlusions, the total number of thrombosed veins was 2468. The data indicated that the most commonly thrombosed vessel was the femoral vein (51.7%), followed by the ili vein (20.3%), the calf vein (12.2%) and popliteal vein (12.2%), and the subclavian vein (3.73%) (Fig. 1). The ratio between right- and left-sided occlusions was 37.2% vs. 62.8% for ili veins, 47.7% vs. 52.3% for femoral veins, 46.3% vs. 53.7% for popliteal veins, 46.2% vs. 53.8% for calf veins, and 55.4% vs. 44.6% for subclavian veins. A very similar pattern of distribution was recorded in Group D which comprised 1438 patients (1453 thromboses) who received fibrinolytic therapy and had undergone phlebography prior to treatment. The one exception was the much lower incidence of calf vein thrombosis in Group D compared with the unselected cohort (2.48% vs. 12.2%) (Fig. 1).

**Fibrinolytic Therapy**

The following forms of fibrinolytic therapy were used (Table 3):