ORIGINAL RESEARCH ARTICLE

Tanaffos (2003) 2(5), 15-22

The Study of Diagnosed Venous Thromboembolism

Enayat Safavi, Mohammad Reza Zahedpour Anaraki, Shahram Firoozbakhsh, M Nikparvar Fard

Department of Internal Medicine, Pulmonary Division, Imam-Khomeini Hospital, Tehran University of Medical Sciences and Health Services, TEHRAN- IRAN

ABSTRACT

***Background**: Pulmonary Thromboembolism (PTE) is the most common preventable cause of death in European and North American hospitalized patients. There are some differences in Venous Thromboembolism (VTE) epidemiology among different populations. This study was performed to determine the hospital incidence and case fatality rate of VTE and its association with risk factors.*

***Materials and Methods**: Careful reviewing of records of all patients discharged during an 8-year period (1989-1997) with the diagnosis of Deep Vein Thrombosis (DVT) and/or PTE.*

***Results**: There were 70 patients with PTE and 140 with DVT. The hospital incidence of VTE was 9 per 10/000. The mean age was 41 and female/male ratio was 1.6. One or more risk factors for VTE were present in 95% of patients, two or more in 67%. The most common ones were age>40 years (45%), prolonged immobility (29%), pregnancy or puerperium (28%), major surgery (16%), and history of VTE (16%). No patient had received DVT prophylaxis. Case fatality rate of PTE was 11%.*

Conclusion**: The hospital VTE incidence is much lower than Western counterparts. The most important reasons may be youthfulness of Iran population and probably their hematological profiles. As the populations mean age is increasing, VTE incidence may be much higher in the future. Our study confirms earlier reported risk factors. Because of high birth rate, pregnancy and puerperium are among the most important risk factors. Prophylaxis for VTE is highly underused by our physicians. Clinical features and mortality rate conform well to western reports.* ***(Tanaffos 2003; 2(5): 15-22)

***Key words**: Deep vein thrombosis, Pulmonary thromboembolism, Incidence, Risk factors, Mortality*

INTRODUCTION

Venous thromboembolism (VTE) includes two related diseases: 1) deep vein thrombosis (DVT) and 2) pulmonary thromboembolism (PTE). Virchow proposed three basic factors including stasis of blood flow, intimal injury, and hypercoagulability which lead to thrombus formation. Virchow triad remains the foundation of PTE pathogenesis and mechanism of risk factor's action. It is unusual for a patient to develop PTE in the absence of any risk factor (1). In a review of 1231 patients treated for VTE, 96% had one or more recognized risk factors (2). It is evident

Correspondence to: Safavi E
Tel.: +98-912-1099170
E-mail address: enayatsafavi@hotmail.com

that risk of VTE has a direct relationship to the number of predisposing factors (1,3,4).

The total incidence and fatality rates for VTE are uncertain because signs and symptoms caused by VTE are nonspecific and may be confused with a variety of other cardiopulmonary disorders that have similar presentation (5,6). PTE is the most common preventable cause of death in European and North American hospitalized patients and causes 10% of hospital mortality (7-9). However, there are some studies that determine a low incidence of VTE in the Far East (10-12). About two third of fatal PTE has not been recognized and changed over 3 decades (13). As diagnosis and treatment of PTE are difficult and expensive, the most effective means for reducing its mortality is establishing prophylactic regimens for DVT. Despite long-standing convincing evidence of the efficacy and safety of a number of prophylactic agents (14,15), only a minority of patients who fulfill criteria for moderate or high risk of VTE receive any forms of prophylaxis (16,17). The most important step in VTE prevention is recognition of predisposing factors and high risk individuals (4,14).

This study provides an estimate of epidemiology of VTE with associated risk factors in Iran.

MATERIALS AND METHODS

The study population constituted all patients discharged during an 8-year period from March 21,1989 to June 22, 1997, with a diagnosis of DVT and/ or PTE from Imam Khomeini hospital. Medical records were individually reviewed and validated based on hospital discharge diagnosis selected from the International Classification of Diseases Ninth Revision (ICD-9-CM) codes for DVT-451.2, 451.11, 451.19, 451.81, 453.2, 453.8, 453.9, 671.30, 671.31, 671.33, 671.40, 671.42, 671.44, 671.9 (0-4), 997.2, 999.2- and codes for PTE- 415.1, 639.6, 673.20, 673.24, 996.7. While all records of the above codes, were reviewed in a systematic manner, data were collected only from records that included a written hospital discharge diagnosis of DVT and / or PTE.

A standard data abstraction form was developed for the medical record review. The form included information on demographic characteristics, risk factors, concurrent medical conditions, diagnostic methods, prophylaxis, signs and symptoms of VTE, and outcome.

Identification of risk factors was based on a careful review of each record, including the discharge summary, admission history, physical examination, nursing, and progress notes. Obesity was defined as more than 20% above the median recommended weight for height (18). Surgery included major operation, where general or epidural anesthesia lasted 30 minutes or more as a risk factor, and VTE had to occur within 30 days after hospital discharge (19). The classification of fractures was limited to the patients who had a hip, leg, or spine fracture. Atrial fibrillation was categorized as organic heart disease. Catheterization included any diagnostic or therapeutic penetration into central venous system. Prolonged immobility was defined as continuous bed rest for 2 days or more.

Patients were categorized as having either DVT or PTE. The category of PTE included individuals with or without accompanying signs and symptoms of DVT. Only the last episode of patients with recurrent VTE was accounted. The data were analyzed by the authors in a standard manner (20).

RESULTS

There were 232000 acute-care discharges from Imam-Khomeini hospital during the 8-year study period, of which 210 had a discharge diagnosis of DVT and/or PTE. The characteristics of this group are summarized in table 1. Prophylaxis against VTE had not been provided to any of them. The mean age was 41 years. The male patients were about 10 years

older than females. The mean age of patients with PTE was 5 years older than DVT.

Table 1. Characteristics of 210 patients with Deep vein Thrombosis and/or Pulmonary Thromboembolism

Characteristic	DVT	PTE
Age (mean) year	39	44
Male (year)	48	46
Female (year)	35	42
Male %	34%	47%
Objectively proven	93(66%)	57(81%)
Pulmonary perfusion scan (PPS)	No	48(69%)
Two segmental or greater defect in PPS	No	37(53%)
Subsegmental defect in PPS	No	11(16%)
Detection of DVT by doppler	93(66%)	31(44%)
Prophylaxis use	No	No
Death	No	8(11%)

One or more signs or symptoms suggestive of DVT (Table 2) or PTE (Table 3) were found in 100% of patients. 93(66%) out of 140 patients with DVT diagnosis were objectively confirmed by doppler. Among the 70 patients with PTE diagnosis, 57 (81%) were objectively confirmed by two segmental or greater defect in pulmonary perfusion scan (53%) and/or doppler diagnosis of DVT (44%). Restricting diagnosis to objectively confirmed cases proportionately reduces the incidence rates of VTE; however, the shape of the age distribution and other results are essentially unchanged.

Table 2. Sings or symptoms observed in 140 patients with deep vein thrombosis

Sign or Symptom	%
Swelling	100
Pain	95
Tenderness	70
Warmth	51
Redness	40

Table 3. Signs or symptoms observed in 70 patients with pulmonary thromboembolism

Sign or Symptoms	%
Dyspnea	88
Tachypnea	84
Chest pain	80
Tachycardia	68
Arterial PO2< 60 mmHg	49
Rale	35
Elevated JVP	32
S3 gallop	30
Hemoptysis	24
Fever < 38.5	23
Right ventricular strain	19
Pleural friction rub	17
Syncope	10
Right bundle branch block	10
Symptoms or signs of DVT	43

The prevalence of risk factors in 210 patients with VTE are shown in table 4.

Table 4. Risk factors in 210 patients with Venous Thromboembolism (VTE)

Risk Factor	VTE, % (N=210)
Age 40 years or more	45
Prolonged immobility	29
Pregnancy	20
History of venous thromboembolism	16
Major surgery	16
Obesity	10
Fracture (hip, leg, spine)	9
Estrogen treatment	9
Congestive heart failure	9
Puerperium	8
Organic heart diseases	7
Cancer	5
Autoimmune diseases	4
Catheterization	2
Myocardial infarction	2
Stroke	2
1 or more risks	95
2 or more risks	67
3 or more risks	31

Among autoimmune diseases, Behcet's syndrome (4 patients) and lupus anticoagulant syndrome (2 patients) were noticeable. Eleven patients had cancer including colon and rectum, gall bladder, breast, testes, prostate, and leukemia. The most common organic heart disease was mitral stenosis. In addition, VTE complications occurred within 20 days of puerperium and 14 days after myocardial infarction. 33 patients developed VTE within 40 days after a major surgery. All of them had other risk factors in addition to surgery. The most common types of surgery were orthopedic, obstetric & gynecologic, and cancer (table 5).

Table 5. Type of surgery in patients with venous thromboembolism

Operation	No
Orthopedic	8
Obstetric	8
Cancer	6
Gynecologic	2
Open heart surgery	2
Neurosurgery	2
Other	5

Two or more risk factors were present in 67% of patients, and only 5% had no apparent risk factor. The average number of risk factors for every patient with VTE, DVT and PTE was 2, 1.9 and 2.2, respectively. The calculation of risk factors was according to those mentioned in table 4 and other probable risk factors were not considered.

In-hospital mortality rate of PTE was 11%. The eight patients who died from PTE had averagely four risk factors, and their mean age was 45 years old. Their most common risk factors were the age 40 years or more, history of VTE, and Surgery.

DISCUSSION

VTE hospital incidence was 9 per 10/000 admission while it was 90 per 10/000 in the United States (21). Although this ratio can not exactly predict the population based on annual incidence of VTE, documents its relative infrequency or under diagnosis in Iran. Many factors probably contribute to this relatively low incidence. There is an association between increasing age and a higher incidence of VTE (22,23). A 1986 community wide study based on data abstracted from medical records in Massachusetts (The Worcester VTE study) (21) showed that the incidence increased exponentially with age by a factor of 200 between 20 and 80 years of age. The population of Iran is young while about 43% of people in West are aged 40 years old or more, only 18% of Iranians are (24, 25). This youthful demographic distribution results in not only a low incidence but also a low mean age of patients, as in this study, which is about 25 years younger than Western counterparts. However, the mean age of Iran population is on the increase and we predict that VTE incidence will be much higher in the future. The influences of race and geographic area on VTE have also been reported. DVT has a lower incidence in a black Caribbean population than North American blacks (26).

Activated protein C resistance is another important issue. Factor V Leiden is the most common inherited venous thrombophilia. Although this factor initially detected in 60% of selected patients with VTE, subsequent studies have detected this mutation in 10%-20% of unselected patients with VTE (27, 28). Factor V Leiden is relatively common in those of European background (approximately 5% of whites in Europe are heterozygous for this genetic defect) but rare in those of African or Asian origin (28-31).

Other possible causes of low incidence of VTE in Iran are regional differences including major known risk factors (cancer, surgery, estrogen therapy, obesity), hyperlipidemia (32), alcohol abuses (1,3), fibrinolytic activity (33), susceptibility to anticoagulating agents (34), and physical activity. Our findings stimulate more interest in the comparative study of the Iranian hematological profile and ethnic particulars.

Without a non-PTE, non-DVT control group with exact histories, we are unable to comment on the relative risk conferred by various factors. Averagely, every patient had 2 risk factors, and only 5% of patients had no apparent one. Because retrospective studies underestimate the positive statistic, the real percent of patients with no risk factor may be lower. This clarifies the significance of detecting risk factors to determine the high risk group and beginning prophylaxis for them. Unfortunately, prophylaxis against VTE is highly underused between our physicians and no patient had been received it. The use of prophylaxis will improve if physicians participate in a continuing medical education program on the prevention of VTE (35). Iran crude birth rate was high (35/1000 in 1994) (24) and this made pregnancy as a major risk factor. Pregnancy or puerperium was present in 45% of female patients. This results in a lower mean age of female patients and a higher female to male ratio (1.6) than Western counterparts (1/1) (21). A study in Assir region of Saudi Arabia showed about the same results (36). The clinical features of patients conform well to those reported in the West, but perhaps appeared in a more symptomatic form, which may result from infrequent performing the autopsy and screening test for VTE.

In-hospital mortality rate, observed in this study, appears similar to those reported in controlled clinical trials in major academic health centers (21, 37). The presence of average four risk factors per patient who died from PTE, denotes that the more risk factors, the higher probability and mortality of PTE. How much this increase in mortality results from accompanying risk factors themselves or from severity of PTE is still unclear; however, probably both of them contribute to it. This fact obligates more attention to prophylaxis with more risk factors in a patient.

REFERENCES

1. Nylander G, Olivercrona H, Hedner U. Earlier and concurrent morbidity of patients with acute lower leg thrombosis. ***Acta Chir Scand*** 1977; 143(7-8): 425-9.
2. Anderson FA Jr, Wheeler HB. Physician practices in the management of venous thromboembolism: a community-wide survey. ***J Vasc Surg*** 1992; 16(5): 707-14.
3. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A Prospective study of the incidence of deep-vein thrombosis within a defined urban population. ***J Intern Med*** 1992; 232(2): 155-60.
4. Arcelus JI, Candocia S, Traverso CI, Fabrega F, Caprini JA, Hasty JH. Venous thromboembolism prophylaxis and risk assessment in medical patients. ***Semin Thromb Hemost*** 1991; 17S3: 313-8.
5. Goldhaber SZ, Hennekens CH, Evans DA, Newton EC, Godleski JJ. Factors associated with correct antemortem diagnosis of major pulmonary embolism. ***Am J Med*** 1982; 73(6): 822-6.
6. Bergqvist D, Lindblad B. A 30-year survey of pulmonary embolism verified at autopsy: an analysis of 1274 surgical patients. ***Br J Surg*** 1985; 72(2): 105-8.
7. Daisley H. Pulmonary embolism as a cause of death. ***West Indian Med J*** 1990; 39(2): 86-90.
8. Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients. Are we detecting enough deep vein thrombosis? ***J R Soc Med*** 1989; 82(4): 203-5.

9. Rubinstein I, Murray D, Hoffstein V. Fatal pulmonary emboli in hospitalized patients. An autopsy study. ***Arch Intern Med*** 1988; 148(6): 1425-26.
10. Woo KS, Tse Lk, Tse CY, Metreweli C, Vallance-Owen J. The prevalence and pattern of pulmonary thromboembolism in the Chinese in Hong Kong. ***Int J Cardiol*** 1988; 20(3): 373-80.
11. Cunningham IG, Yong NK. The incidence of postoperative deep vein thrombosis in Malaysia. ***Br J Surg*** 1974; 61(6):482-3.
12. Hwang WS. The rarity of pulmonary thromboembolism in Asians. ***Singapore Med J*** 1968; 9(4): 276-9.
13. Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at an autopsy. ***Chest*** 1995; 108(4): 978-81.
14. Anderson FA Jr, Wheeler HB. Venous thromboembolism. Risk factors and prophylaxis. ***Clins Chest Med*** 1995; 16(2): 235-51.
15. Oster G, Tuden RL, Colditz GA. Prevention of venous thromboembolism after general surgery, cost-effectiveness analysis of alternative approaches to prophylaxis. ***Am J Med*** 1987; 82(5): 889-99.
16. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Forcier A, Patwardhan NA. Physician practices in the prevention of venous thromboembolism. ***Ann Intern Med*** 1991; 115(8): 591-5.
17. Valles JA, Vallano A, Torres F, Arnau JM, Laporte JR. Multicentre hospital drug utilization study on the prophylaxis of venous thromboebolism. The Venous Thromboembolism Study Group of the Spanish Society of Clinical Pharmacology. ***Br J Clin Pharmac*** 1994; 37(3): 255-9.
18. American medical association. AMA height- weight table. 3th ed. Chicago: American medical association, 1975.
19. Huber O, Bounameaux H, Borst F, Rohner A. Postoperative pulmonary embolism after hospital discharge. An underestimated risk. ***Arch Surg*** 1992; 127(3): 310-3.
20. Lawless JF. Statistical models for lifetime Data. New York, NY: John Wiley & Sons Inc, 1982.
21. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case- fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT study. ***Arch Intern Med*** 1991; 151(5): 933-8.
22. Hansson PO, Welin L, Tibblin G, Eriksson H. Deep vein thrombosis and pulmonary embolism in the general population. The Study of Men Born in 1913. ***Arch Intern Med*** 1997; 157(15): 1665-70.
23. Kniffin WD Jr, Baron JA, Barrett J, Birkmeyer JD, Anderson FA Jr. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. ***Arch Intern Med*** 1994; 154(8): 861-6.
24. Statistical center of Iran. Iran statistical yearbook 1375. Tehran: Statistical center of Iran, 1375: 39.
25. World health organization. World Health statistical annual 1995. World health organization 1995: A3-A9.
26. Nossent JC, Egelie NC. Incidence and course of symptomatic deep venous thrombosis of the lower extremities in a black Caribbean population. ***Thromb Haemost*** 1993; 70(40): 576-8.
27. Svensson PJ, Dahlback B. Resistance to activated protein C as a basis for venous thrombosis. ***N Engl J Med*** 1994; 330(8): 517-22.
28. Fedullo PF. Pulmonary Thromboembolism. In: Murray & Nadel, Textbook of respiratory medicine. Third ed. Philadelphia: Saunders; 2000. P. 1504.
29. Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women. Implications for venous thromboembolism screening. ***JAMA*** 1997; 277(16): 1305-7.
30. Gregg JP, Yamane AJ, Grody WW. Prevalence of the factor V-Leiden mutation on four distinct American ethnic populations. ***Am J Med Genet*** 1997; 73(3): 334-6.

31. Pepe G, Rickards O, Vanegas OC, Brunelli T, Gori AM, Giusti B, et al. Prevalence of factor V Leiden mutation in non-European populations. ***Thromb Haemost*** 1997; 77(2): 329-31.

32. Kawasaki T, Kambayashi J, Sakon M. Hyperlipidemia; a novel etiologic factor in deep vein thrombosis. ***Thromb Res*** 1995; 79(2): 147-51.

33. Feanley GR. A Concept of natural fibrinolysis. ***Lancet*** 1961; 1: 992-3.

34. Poller L, Taberner DA. Dosage and control of oral anticoagulants: an international collaborative survey. ***Br J Haematol*** 1982; 51(3): 479-85.

35. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Forcier A, Patwardhan NA. Changing clinical practice. Prospective study of the impact of continuing medical education and quality assurance programs on use of prophylaxis for venous thromboembolism. ***Arch Intern Med*** 1994; 154(6): 669-77.

36. Igbinovia A, Malik GM, Grillo LA, Seidi OA, Egere JU, Hachem MM, et al. Deep venous thrombosis in Assir region of Saudi Arabia, case-control study. ***Angiology*** 1995; 46(12): 1107-13.

37. Alpert JS, Smith R, Carlson J, Ockene IS, Dexter L, Dalen JE. Mortality in patients treated for pulmonary embolism. ***JAMA*** 1976; 236(13): 1477-80.