

Delays in diagnosis and treatment of venous thromboembolism in a developing country setting

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ÖZET

Gelişmekte olan bir ülkede venöz tromboembolizm tanısı ve tedavisindeki gecikmeler

Giriş: Derin ven trombozu ve pulmoner tromboembolizmin hızlı tanısı ve tedavisi mortalite ve morbiditeyi azaltmaktadır. Bu çalışmanın amacı, gelişmekte olan bir ülkede, derin ven trombozu ve pulmoner tromboembolizm tedavisindeki gecikmeleri ve ilişkili faktörleri araştırmaktır.

Materyal ve Metod: Urmia, İran'da derin ven trombozu ve/veya pulmoner tromboembolizm tanılı 353 hasta prospektif olarak çalışıldı. Semptomların başlangıç tarihi, klinisyen tarafından yapılan ilk değerlendirme, tedavi başlangıcı ve tanının doğrulanma bilgileri kaydedildi. Ayrıca, bazı faktörlerle ilişkisi incelendi.

Bulgular: Semptomların başlangıcından tedavi başlanmasına kadarki ortalama süre 4.70 gündü, bu sürenin %89'u semptomların başlangıcından ilk medikal değerlendirmeye kadar geçen süreydi (ortalama= 4.19 gün). Semptomların başlangıcından tanının doğrulanmasına kadarki ortalama süre 6.29 gündü. Venöz tromboembolizimli 353 hastanın 185 (%52.4)'i semptomların başlangıcından sonra ilk iki günde, 168 (%47.6)'i iki günden sonra bir klinisyen tarafından değerlendirildi. Erken değerlendirme ile ilişkili olan ve p değeri < 0.05 olan faktörler; yüksek eğitim düzeyi, yakın zamanda cerrahi, alçı varlığı, bacakta şişme ve pulmoner tromboembolizimli hastaların derin ven trombozlu hastalara göre daha erken değerlendirildiği saptandı. Yaş, cinsiyet, semptom sayısı ve venöz tromboembolizm yönünden aile öyküsü ile ilişki yoktu (p> 0.05). Yüksek olasılık skorlu hastalarda ilk değerlendirmeden tanıya kadar geçen süre anlamlı olarak daha kısaydı.

Sonuç: Venöz tromboembolizimli hastaların çoğunda tanısı ve antikoagülasyon tedavide gecikme vardı. Gecikmenin başlıca nedeni hasta ile ilişkiliydi. Hastaların venöz tromboembolizm konusunda farkındalığını artıracak ve gecikmeyi kısaltacak stratejilere ihtiyaç bulunmaktadır.

Anahtar Kelimeler: Pulmoner tromboembolizm, derin ven trombozu, risk faktörleri, tanıda gecikme.

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SUMMARY***Delays in diagnosis and treatment of venous thromboembolism in a developing country setting***

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Introduction: Rapid diagnosis and treatment of deep vein thrombosis and pulmonary thromboembolism reduce mortality and morbidity. The aim of this study is to investigate delays in treatment of deep vein thrombosis and pulmonary thromboembolism and related factor in a developing country.

Materials and Methods: We prospectively investigated 353 patients with diagnosis deep vein thrombosis and/or pulmonary thromboembolism in Urmia, Iran. We recorded dates of symptom onset, initial visit by a clinician, initiation of treatment, and confirmation of diagnosis. We also analyzed relation with some factors.

Results: The mean interval from symptoms onset to initiation of treatment was 4.70 days, 89% of this interval was between onset of symptoms to first medical evaluation (mean= 4.19 days). Mean time from onset of symptoms to confirmation of diagnosis was 6.29 days. Of 353 patients with venous thromboembolism 185 (52.4%) visited by a physician within two days of onset of symptoms and 168 (47.6%) patients after two days. Factors that was associated with earlier seeking with p value < 0.05 were pulmonary thromboembolism patients earlier than deep vein thrombosis, higher education, recent surgery, presence of cast, entire leg swelling. There was no association between age, gender, number of symptoms, and presence familial history of venous thromboembolism (all p value > 0.05). The delays time from first visit to final diagnosis was significantly shorter in patients with high probability score.

Conclusion: Most patients with venous thromboembolism received anti-coagulation and diagnosis with delay. The main cause of delay is related to patient's delays. There is a need to improve people awareness about venous thromboembolism and to develop strategies to reduce delays.

Key Words: Pulmonary thromboembolism, deep vein thrombosis, risk factors, delayed diagnosis.

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INTRODUCTION

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) are acute disease. Acute PTE is the cause of 50.000 to 200.000 death annually in the USA (1). Its mortality reported to be about 13% in first month and 35.3% within three years after diagnosis. As many as 95% of PTE related deaths occur prior to diagnosis or within hours of the event (2-4). One study showed that patients diagnosed within 48 hours had better outcomes (5).

Despite the stated facts about VTE, delays in diagnosis and initiating treatment are a common problem. A study in USA reported delays in diagnosis in approximately 20% of patients with VTE. However, data about delays in the diagnosis of VTE in a developing country are sparse.

The aim of this study is to determine delays in diagnosis and treatment of VTE, and related factors in a developing country setting.

MATERIALS and METHODS

We prospectively investigated 353 consecutive patients with imaging confirmed diagnosis DVT and/or PTE from May 2008 to August 2012. It was conducted at Imam Khomeini Hospital, a tertiary care hospital at Urmia University of Medical Sciences (Iran). It was approved by the university research council. The following information was collected:

- a. Demographic data: i.e., age, sex, level of education,
- b. Dates includes: the date of symptom onset, the date that the subject was first seen by medical personnel for these symptoms, the date that VTE treatment initiated, and the date on which the diagnosis was confirmed with imaging,
- c. Presence of temporary risk factors for VTE at the time of symptoms onset and their relation with delays,
- d. DVT or PTE probability scoring parameters on the day of admission to our center score (6,7).

Definition of Terms

1. Patients delay: Interval in days between onsets of symptoms to first seeking medical attention. It categorized as early, visit within two days of onsets of symptoms and late: after second day of symptoms onset.

2. Diagnosis delay: Interval in days between first day seeking medical attention to final confirmatory imaging. It categorized as early, confirmation within first two days and late after second day of first seeking medical help.

3. Total diagnosis delay: Interval in days between first onsets of symptoms to final confirmatory imaging.

4. Delay in treatment, interval between onset of symptoms and initiation anti-coagulation.

Statistical Analysis

SPSS version 18 software is used. Baseline characteristics are reported by descriptive analysis. Chi-square test is used to analyze the difference in frequencies between two groups. p values < 0.05 are considered to be significant.

RESULTS

In this study 353 patients VTE (234 patients DVT only, 88 patients PTE only, 31 patients both PTE and DVT) were studied. The mean age of patients was 54.46 years. Of patients 199 (56.4%) were male and 154 (43.6%) were female. Table 1 shows baseline characteristics of patients.

Mean interval from symptoms onset to initiation of treatment was 4.70 days, 89% of it was interval between onset of symptoms to first medical evaluation (mean= 4.19 days, for PTE patients 3.05 SD= 6.42 days for DVT patients 4.61 Sd= 5.78, and p= 0.037). Mean time from onset of symptoms to final diagnosis was 6.29 days. Most patents had initiation of treatment before confirmation of diagnosis, the mean time from first visit to final diagnosis 2.09 days and to beginning of treatment was 0.50 days. The Table 2 summarizes inter-

vals time and Figure 1 shows distribution of time from onset of symptoms to first visit by a physician.

Of 353 patients, 90 (25.5%) patients found medical attention on the day of onset of symptoms, 298 (84.4%) received anticoagulation on first day of visit by physician and 195 (55.2%) had VTE confirmation on first day of visit.

Of 264 patients with DVT 52 (22.2%) found medical advice on the day of event and 58 (25%) patients after one week while patients with PTE 38 (31.9%) on day of symptom onset 16 (13.4%) after one week visited by a physician.

Of 353 patients with VTE 185 (52.4%) visited by a physician within two days of onset of symptoms and 168 (47.6%) patients visited after two days.

The comparison of related factors for these two groups is shown in Table 3. We found no difference in the gender and in the mean age of the two groups. The-

Table 1. Demographic data of 353 patients.

| Variable | n (%) |
|-----------------------|---------------|
| Age mean ± SD (years) | 54.46 ± 17.27 |
| Sex | |
| Male | 199 (56.4) |
| Female | 154 (43.6) |
| Diagnosis | |
| DVT | 234 (66.3) |
| PTE | 88 (24.9) |
| DVT and PTE | 31 (8.8) |
| Education level | |
| Illiterate | 196 (55.5) |
| Primary school | 46 (13.0) |
| Guidance | 17 (4.8) |
| High school | 42 (11.9) |
| University | 26 (7.4) |

Table 2. Timing intervals in days for delays.

| | Mean ± Std. | Median | Maximum |
|---|-------------|--------|---------|
| Interval from onset of symptoms to first visit in days | 4.19 ± 5.87 | 2.00 | 45 |
| Interval from first visit to confirmation of diagnosis in days | 2.09 ± 4.12 | 0.00 | 26 |
| Total interval from onset of symptoms to final diagnosis | 6.29 ± 7.28 | 4 | 65 |
| Interval of first visit to beginning of treatment in days | 0.50 ± 3.38 | 0.00 | 60 |
| Interval from onset of symptoms to beginning of treatment in days | 4.70 ± 6.70 | 3.0 | 60 |

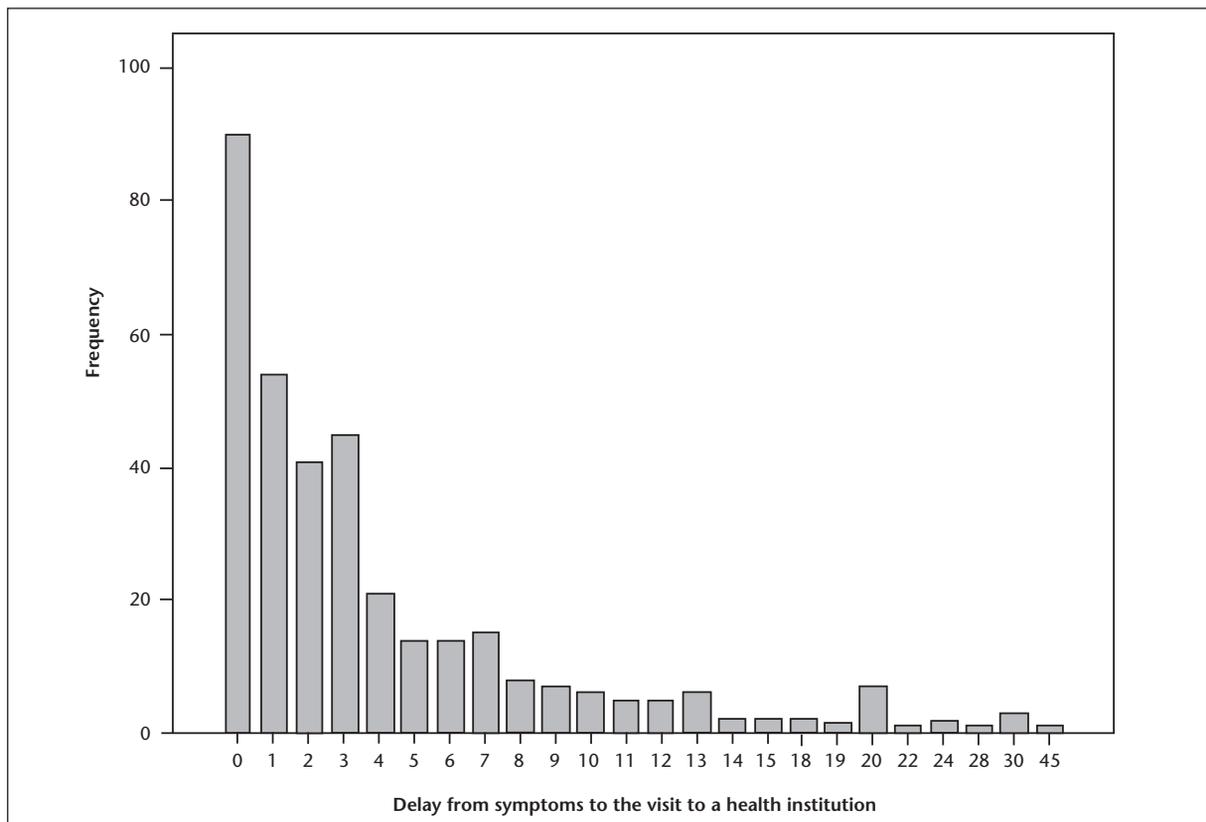


Figure 1. Delays in days from onset of symptoms to first visit by a physician (0 means on the same day of onset of symptoms, 1: One day later, 2: Two days later, ...).

re was also no statistically significant difference in the timing of seeking medical attention between patients younger than 40 year and patients older than 40 years. Patients with higher education level evaluated and diagnosed earlier. Patients with PTE had medical evaluation earlier than patients with DVT alone ($p=0.003$).

We recorded clinical probability of DVT and PTE on the day of admission to our center. The mean DVT probability score in 170 patients with final diagnosis of DVT within first two days of visit was 4.09 ± 1.32 and for 64 patients after the first two visit day was 3.20 ± 1.61 ($p < 0.001$). Table 4 summarized relation of diagnosis delay from first seeking medical attention to scoring system parameters, Bedridden or surgery, tenderness along distribution of deep veins, and pitting edema was significantly associated with early diagnosis ($p < 0.005$). Patients with high probability for DVT had significantly earlier diagnosis than those with low probability for DVT ($p = 0.001$). The mean Wells score in 71 patients with final diagnosis of PTE within first two days of visit was 5.33 ± 2.55 and for 47 patients with final diagnosis after the first two visit day was 3.96 ± 2.55 ($p = 0.006$).

Patients with Wells probability score intermediate and high had earlier diagnosis than those with low probability ($p = 0.024$). Table 5 summarized diagnosis delay relation to Wells PTE probability scoring parameters.

DISCUSSION

Our study shows that mean interval between onsets of VTE symptoms to initiation of treatment is near to five days. This is while that it has been confirmed that early diagnosis and treatment reduces mortality for acute PTE (8). It may also decrease the development of the post-phlebitis syndrome, and, chronic pulmonary hypertension following PTE (9,10). Non-specific symptoms and signs of VTE mimic other illnesses, and PTE is known as "the Great Masquerader," making diagnosis difficult even for experienced physicians.

In current study, most of the delay in the diagnosis and treatment of VTE represented the delay from symptom onset to the date of first medical evaluation. To our knowledge there are two studies that evaluated delay both DVT and PTE. In a study by Elliot et al., with studying of 1152 patients with VTE (DVT $n = 808$, PTE $n = 344$) in North American hospitals, reported that the mean delay from symptom onset to medical attention

Table 3. Comparison early (n= 185) and delayed (n= 168) for medical evaluation from onset of VTE symptoms.

| Variable | Early* | Delayed* | Total | p |
|-------------------------------------|-------------|-------------|-------|-------|
| Sex | | | | |
| Male | 101 (50.8%) | 98 (49.2%) | 199 | 0.48 |
| Female | 84 (54.5%) | 70 (45.5%) | 154 | |
| Education | | | | |
| Illiterate or less than high school | 132 (49.3%) | 136 (50.7%) | 268 | 0.035 |
| High school and university | 53 (62.4%) | 32 (37.6%) | 85 | |
| Age less than 40 years | 62 (56.9%) | 47 (43.1%) | 109 | 0.26 |
| Age 40 years or more | 123 (50.4%) | 121 (49.1%) | 244 | |
| DVT | 110 (47.0%) | 124 (53.0%) | 234 | 0.003 |
| PTE with or without DVT | 75 (63.0%) | 44 (37.0%) | 119 | |
| Chronic respiratory disease | 16 (43.2%) | 21 (56.8%) | 37 | 0.238 |
| Previous DVT or PTE | 25 (56.8%) | 19 (43.2%) | 44 | 0.531 |
| Familial history of DVT or PTE | 12 (57.1%) | 9 (42.9%) | 21 | 0.654 |
| Presence of cancer | 21 (47.7%) | 23 (61.8%) | 34 | 0.506 |
| Cardiac disease | 13 (28.2%) | 21 (61.8%) | 34 | 0.082 |
| Cerebrovascular disease | 16 (45.7%) | 19 (54.3%) | 35 | 0.403 |
| Pregnancy | 9 (56.4%) | 7 (43.8%) | 16 | 0.753 |
| Paralysis | 7 (38.9%) | 11 (61.1%) | 18 | 0.238 |
| Surgery | 58 (66.7%) | 29 (33.3%) | 87 | 0.002 |
| VTE prophylaxis | 21 (58.3%) | 15 (41.7%) | 36 | 0.453 |
| Postphlebitis syndrome | 8 (44.4%) | 10 (55.6%) | 18 | 0.487 |

* Early: Within 2 days of onset of symptoms; Delayed: More than 2 days after onset of symptoms.

Table 4. DVT score of patients with DVT and its relation to interval to final diagnosis from first day of seeking medical attention.

| Variable | Score ⁽⁶⁾ | Early* | Delayed* | Total | p |
|--|----------------------|-------------|------------|-------|-------|
| Active cancer | 1 | 27 (81.8%) | 6 (18.2%) | 33 | 0.143 |
| Paralysis, paresis, or recent cast | 1 | 19 (76.0%) | 6 (24.0%) | 25 | 0.69 |
| Bedridden for > 3 days; major surgery < 12 weeks | 1 | 101 (81.5%) | 23 (18.5%) | 124 | 0.001 |
| Tenderness along distribution of deep veins | 1 | 134 (77.9%) | 38 (22.1%) | 172 | 0.003 |
| Entire leg swelling | 1 | 140 (75.3%) | 46 (24.7%) | 186 | 0.77 |
| Unilateral calf swelling > 3 cm | 1 | 120 (76.4%) | 37 (23.6%) | 157 | 0.064 |
| Pitting edema | 1 | 125 (77.2%) | 37 (22.8%) | 162 | 0.020 |
| Collateral superficial non-varicose veins | 1 | 30 (71.4%) | 12 (28.6%) | 42 | 0.84 |
| Alternative diagnosis at least as likely as DVT | -2 | 0 | 0 | 0 | Not |
| Low probability DVT** | | 17 (48.6%) | 18 (51.4%) | 35 | |
| High probability for DVT** | | 153 (76.9%) | 46 (23.1%) | 199 | 0.001 |

* Early: Confirmation of diagnosis within first 2 days of seeking medical attention; Delayed: More than 2 days after onset of symptoms (by definition in this study).

** A score of two or higher indicates that the probability of deep-vein thrombosis is likely; a score of less than two indicates that the probability of deep-vein thrombosis is unlikely (6).

Table 5. Relation of delay from first visit to final diagnosis to PTE score.

| Clinical variable | Score | Early* n (%) | Delayed* n (%) | Total n (%) | p |
|---|-------|-----------------|-------------------|----------------|-------|
| Signs and symptoms of DVT | 3.0 | 27 (69.2) | 12 (30.8) | 39 (32.8) | 0.137 |
| Alternative diagnosis less likely than PE | 3.0 | 53 (67.9) | 25 (32.1) | 78 (64.3) | 0.011 |
| Heart rate > 100/min | 1.5 | 33 (70.2) | 24 (29.8) | 47 (39.5) | 0.058 |
| Immobilization > 3 days; surgery within 4 weeks | 1.5 | 34 (66.7) | 17 (33.3) | 51 (42.9) | 0.177 |
| Prior PE or DVT | 1.5 | 12 (60.0) | 8 (40.0) | 20 (16.8) | 0.973 |
| Hemoptysis | 1.0 | 13 (44.8) | 16 (55.2) | 29 (24.4) | 0.061 |
| Cancer | 1.0 | 6 (75.0) | 2 (25.0) | 8 (6.7) | 0.301 |
| Wells PTE probability low** vs. | | 10 (40.0) | 15 (60.0) | 25 | 0.024 |
| Well probability intermediate and high** | | 61 (64.9) | 33 (35.1) | 94 | |

* Early: Confirmation of diagnosis within first 2 days of seeking medical attention, delayed: more than 2 days after onset of symptoms (By definition in this study).

** A point score < 2: low probability, 2-6 points intermediate probability, and > 6 points high probability.

was 2.9 days, which is shorter than the current study (4.19 days)(11). In second study by Ageno et al., among 2047 patients (1505 with DVT and 542 with PTE) 64.0% patients with PTE 47.1% with DVT had diagnosis less than five days (16).

In a study in Turkey the mean time from symptoms onset to the first admission to a health institution among patients with PTE was about 2.04 days which were shorter than our study for PTE patients (3.05 days) (12).

In a study by Jimenez Castro, of the 397 patients with acute PTE, 72 (18%) had a diagnostic delay while 325 (82%) did not, the median time from symptom onset to diagnosis was 7 days and 6% patients had a delay of more than 25 days (13).

In Ireland, among 60 patients with PTE near to 50% of patients presented within 24 hours of onset of symptom, and 25% after one week (14). In current study, 31.9% of patients with PTE presented on day of onset of symptoms, which indicate a bad condition in a developing country setting.

A study in Turkey among 156 with PTE showed that, 60.3% of them were admitted to a hospital within the first 24 hours of onset of symptom (12). In our study this rate was lower (22.2% for DVT and 31.9% for PTE).

In our study the delays from the date of first medical evaluation to the start of treatment is shorter than confirmation of VTE. It is an encouraging finding because guidelines recommend initiation of anticoagulation if clinical suspicion for PTE is high, even prior to confirmatory testing (15).

With regarding factors that affect on delays, as expected, first medical evaluation in patients with PTE occurred significantly earlier than those with DVT. It is in line with Ageno et al. study in Italy reported that delayed diagnosis 22.6% patients with DVT and in 16.2% with PTE (16). As also expected, patients with low education level had significantly delays in seeking medical attention. In a study by Bulbul et al. among patients with PTE, a high level of education were associated with longer patient delays, they didn't have explanation for it (12). Our study showed that recent surgery, trauma and cast was associated with earlier seeking medical evaluation. Others also reported similar results (17,18). Similar to a large scale study in Italy (1505 with DVT and 542 with PTE) there was no relation between delays in seeking medical attention with gender, and age (16). Opposite to expectation patients with risk factors for VTE had not significantly earlier seeking medical attention which confirms of unawareness of lay persons about VTE risk factors. It is reported that current smoking and co-morbidity disease are associated with delayed diagnosis (12). We haven't investigated about relation with smoking, but our data did not showed relation with presence of cancer, heart disease, and chronic respiratory disease. We used the Wells scoring systems to determine the pre-test probability that a patient has DVT or PTE. The mean probability score in both DVT and PTE diagnosed in first two days of visit was significantly more than those diagnosed after two days of visit. This is expected and is in line with a study by Alonso-Martinez, where they showed that among 375 patients with PTE, those with a low Wells score show an increased time up to diagnosis (19).

Finding of this study, emphasis importance and essential role of public education for fast diagnosis and treatment of DVT and PTE. Similar to other common and serious disorders such as myocardial infarction, lay persons should learn to suspect for PTE for any unexplained shortness of breath, chest pain.

We conclude that there was a considerable delay from the onset of VTE symptoms to initiation of treatment, patients delays in seeking medical help constitute most part of this delay. Patients with high probability for VTE had earlier diagnosis. We suggest improving lay person's awareness about DVT and PTE, and their alarming symptoms.

CONFLICT of INTEREST

None declared.

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