The predictive factors of recurrent deep vein thrombosis

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Abstract

BACKGROUND: About 2-5% of people experience deep-vein thrombosis (DVT) during their lives. Death, disease recurrence, post-thrombotic syndrome, and excessive bleeding due to coagulant medications are among the most important DVT complications. Recent research found a high incidence of DVT recurrence after the first attack. Disease recurrence has a multifactorial pathogenesis and its probability is related with the number and severity of risk factors. The present study aimed to investigate DVT recurrence and the associated risk factors.

METHODS: This retrospective cross-sectional study evaluated all DVT patients hospitalized in Alzahra Hospital, Isfahan, Iran, during April 2000 to April 2011. The risk factors were obtained from patients' records including smoking, intravenous drug abuse, having a history of surgery in last four weeks, immobility, obesity, history of cardiac disease, and cancer.

RESULTS: A total number of 2550 DVT patients were hospitalized in Alzahra Hospital during the study period. It was only possible to extract the data from 385 patient records. A history of DVT was reported in 48 individuals (12.5%). The comparison between the risk factors in patients with a first time DVT and those experiencing a recurrent DVT revealed significant differences solely in the prevalence of blood disorders and immobility. Applying stepwise regression indicated immobility (OR: 4.57; 95% CI: 1.26-16.57; $P < 0.021$) and coagulopathy (OR: 0.33; 95% CI: 0.13-0.81; $P < 0.016$) with DVT recurrence.

CONCLUSION: Based on our findings, DVT patients are suggested to be mobilized as soon as possible. In addition, they should be advised to increase their activity after discharge.

Keywords: Deep Vein Thrombosis, Immobility, Risk Factor.

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Introduction

Venous thromboembolism (VTE) is the third common vascular disease after coronary artery disease and stroke which is experienced by 2-5% of people during their lifetime. The condition occurs in two forms of deep-vein thrombosis (DVT) and pulmonary embolism (PE).[1-4] The annual rate of DVT with organ involvements in urban areas is reported to be 0.5-1.6 in every 1000 people which is probably much higher in reality due to asymptomatic forms of the disease.[5,6] The risk for DVT increases with age, i.e. while only 5 out of every 100,000 children suffer the problem, the rate increases to 400 out of every 100,000 in people over 80.[7]

Typically, DVT starts with an acute pain, redness and swelling from the calf to the thigh. A clear swelling in the rear thigh with tenderness along the deep venous system is observed in examination. However,in most cases the condition is asymptomatic and silent and heals spontaneously and without treament.[8]

DVT risk factors include aging over 40, obesity, immobilization especially after long journeys, history of hypercoagulation, genetic factors leading to thrombophilia, certain blood diseases, cancer, heart failure, bone fractures, smoking and recent surgeries. In women, however, oral contraceptive pills (OCPs) and hormone replacement therapy (HRT) are also among the main risk factors. In addition, idiopathic form of the disease is not uncommon.[9]

Death, disease recurrence, post-thrombotic syndrome, and severe bleedings are the most important side effects of anticoagulation medicines used for DVT.[10,11] A mortality rate of 6% has been reported in the first six months after the disease onset.[12] Recent studies found a high incidence of recurrent DVT (RDVT) with half of DVT incidences in the U.S being the disease recurrence.[13-18] A relapse after a five-year disease free interval is observed in 20-30% of the patients.[19,20] While some studies reported the annual

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incidence rate of the first recurrent attack to be 3-5%, which is generally most probable to happen during the first two years after the discontinuation of anticoagulation treatment, others claimed a higher rate of 5-10%.[19,21,22] The incidence of disease recurrence, as a condition with a multifactorial pathogenesis, is related with the number and severity of the risk factors. In a study conducted in Norway, cancer, previous proximal DVT and previous VTE were suggested to be major factors causing RDVT. In addition, although the condition is more prevalent among men, many studied did not indicate sex as a risk factor for DVT recurrence.[19]

The present study aimed to investigate the incidence of DVT during 10 years in the main VTE referral center in Isfahan, Alzahra Hospital, and also to find the frequency of reoccurrence and its associated risk factors.

Materials and Methods

This retrospective cross-sectional study investigated all DVT inpatients in Alzahra Hospital during April 2000-April 2011. Patient records were collected from the hospital archive. Patients with incomplete records were excluded. The diagnosis was made based on clinical symptoms, existing risk factors and Doppler sonography.

Demographics, DVT risk factors, clinical symptoms, treatment method, history of DVT, previous treatment for DVT and hospitalization duration were studied in this research. The risk factors included smoking, drug injection, a history of surgery during the last 4 weeks, immobilization, obesity, history of cardiovascular diseases, coagulopathy and cancer. In women, however, additional factors of the history of recent pregnancy, hormone replacement therapy (HRT) and oral contraceptive pill (OCP) usage were also considered.

The data was analyzed in SPSS version 19. Frequency of risk factors, treatment method (percent) and average hospitalization duration (mean ± SD) were calculated. Student's t-test and chi-square test were used to evaluate the risk factors in patients with a history of DVT compared with those experiencing the condition for the first time (FDVT). In order to determine the effective factors in disease recurrence, logistic regression test was employed to calculate odds ratio (OR). A P-value lower than 0.05 was considered statistically significant.

Results

Out of a total number of 2550 patients hospitalized due to DVT during the 11 studied years in Alzahra Hospital, only 385 records were extractable. The average age among the subjects [228 men (59.2%)], was 48.30 ± 19.16 years. No risk factor was found in 35 individuals (9.1%). Most involvements were seen in left leg, in 229 cases alone (59.5%) and in 13 cases with right leg involvements (3.4%). Moreover, the average hospitalization duration was 7.23 ± 5.48 days.

Table 1. The comparison of participants' baseline demographic and risk factors between two groups

Variable	Total n(%)	First DVT n(%)	Recurrent DVT n(%)	P value
n	385(100)	337(87.5)	48(12.5)	
Age (years)*	48.30 ± 19.16	48.79 ± 19.26	44.83 ± 18.28	0.180†
Sex (men)	228(59.2)	200(59.3)	137(40.7)	0.894††
Family history	5(1.3)	4(1.2)	1(2.1)	0.488†††
Coagulopathy	12(3.1)	8(2.4)	4(8.3)	<0.050††
Immobilization	102(26.5)	96(28.5)	6(12.5)	0.019††
smoking	99(25.7)	88(26.1)	11(22.9)	0.635††
surgery	53(13.8)	48(14.2)	5(10.4)	0.472††
Pelvic	9(2.3)	9(2.7)	0	
Knee	2(0.5)	2(0.6)	0	0.837††
Others	42(10.9)	37(11.0)	5(10.4)	
Obesity	7(1.8)	6(1.8)	1(2.1)	1.000†††
Cancer	20(5.2)	18(5.3)	2(4.2)	1.000†††
Contraceptive	38(9.9)	36(10.7)	2(4.2)	0.200†††
HRT	3(0.8)	3(0.9)	0	1.000†††
CVD treatment	17(4.4)	15(4.5)	2(4.2)	0.643
IV drug abuse	32(8.3)	29(8.6)	3(6.3)	0.782††
Pregnancy	8(2.1)	6(1.8)	2(4.2)	0.262††

DVT: Deep vein thrombosis; HRT: Hormone replacement therapy
* Mean ± Standard Deviation; † Student's t-test
†† Chi-square; †††Fisher's exact test

A previous history of DVT existed in 48 subjects (12.5%). Table 1 represents a comparison between demographics and risk factors in FDVT and RDVT groups. As this table shows, although the FDVT group had a higher age, the difference was not significant. In addition, sex distribution in the two groups was similar. The only significant difference among the two groups was observed in the frequency of coagulopathy and immobilization.

Table 2 compares the clinical symptoms, treatment method, and hospitalization duration in FDVT and RDVT groups. Based on this table, swelling was significantly more in FDVT patients than in RDVT subjects. In addition, the hospitalization duration was significantly shorter in RDVT group.

Table 3 represents the model applied to determine the risk factors of RDVT. This model was designed based on regression test using enter method and included all demographics and risk factors. As shown in this table, the calculated odds ratio (OR) was only significant in coagulopathy, immobilization and CVD treatment. Stepwise regression analysis found only immobilization (OR: 4.57; 95% CI: 1.26-16.57; P < 0.021) and coagulopathy (OR: 0.33; 95% CI: 0.13-0.81; P < 0.016) to have a significant relation with RDVT.

Table 2. The comparison of participants' sign and symptoms and the method of treatment between two groups

Variable	Total n(%)	First DVT n(%)	Recurrent DVT n(%)	P value
Site				0.867††
Left Leg	229 (59.48)	202 (59.94)	27 (56.25)	
Right Leg	143 (37.14)	124 (36.79)	19 (39.58)	
Both	13 (3.37)	11 (3.26)	2 (4.16)	
Swelling	374(97.1)	331(98.2)	43(89.6)	0.006††
pain	326(84.7)	288(85.5)	38(79.2)	0.117††
Tenderness	116(30.1)	98(29.1)	18(37.5)	0.234††
Warmness	180(46.8)	163(48.4)	17(35.4)	0.092††
Erythema	93(24.2)	77(22.8)	16(33.3)	0.112††
Bulging	6(1.6)	4(1.2)	2(4.2)	0.165††
fever	27(7.0)	26(7.7)	1(2.1)	0.227††
treatment				
Heparin + warfarin	318(82.6)	275(81.6)	43(89.6)	
Heparin	22(5.7)	20(5.9)	2(4.2)	
Enoxaparin	2(0.5)	2(0.6)	0(0)	0.642††
Enoxaparin + warfarin	27(7.0)	24(7.1)	3(6.3)	
Enoxaparin + warfarin + Heparin	16(4.2)	16(4.7)	0(0)	
Hospital stay (days) *	7.23 ± 5.48	7.43 ± 5.74	5.77 ± 2.64	0.049†

DVT: Deep vein thrombosis; * Mean ± Standard deviation;
† Student's t-test; †† Chi-square

Table 3. The effect of risk factors on the recurrence of deep vein thrombosis

Variable	OR	P value
Age (years)	0.612	0.434
Sex(men)	0.078	0.779
Family history	0.050	0.823
coagolopathy	0.331	<0.016
Immobilization	4.570	<0.021
smoking	0.569	0.451
surgery	0.019	0.891
obesity	0.013	0.908
Cancer	0.073	0.787
HRT	0.276	0.600
CVD treatement	0.001	0.971
IV drug abuse	0.604	0.437
Pregnancy	1.050	0.305

HRT: Hormone replacement therapy
CVD: Coronary vascular disease

Discussion

The prevalence of DVT among men and individuals over 40 years was more than that among women and people below 40. In addition, the third important risk factor (after age and sex) was immobilization.

The regression model showed a significant difference between immobilization and coagulation disorders in patients with first and recurrent DVT. Although immobilization was more common among FDVT patients, stepwise regression showed a significant association between immobilization and RDVT (OR = 4.570). Moreover, hospitalization duration and swelling frequency were significantly less common in RDVT subjects. Kyrle et al. followed 826 patients for 36 months after the first DVT and observed the disease recurrence in 20% of men and 6% of women. Their results indicated a significant relationship between sex and disease recurrence (RR 3.6, 95% CI 2.3-5.5, P < 0.001).[23]

In a meta-analysis conducted on 7 prospective researches, Douketis et al. studied 2554 subjects who were followed for an average of 27.1 months and suggested that compared to women, men were 2.2 times more likely to experience a recurrent VTE after their first DVT. Even after adjusting the model based on HRT in women, recurrent DVT was 1.8 times more common among men.[24] Unlike some previous studies, our findings did not suggest any relation between sex and DVT recurrence (maybe because this was a retrospective study conducted on patients with RDVT).

Cushman et al. studied the occurrence of DVT and pulmonary embolism in 21680 subjects over 45 years that participated in two cohort studies, namely Atherosclerosis Risk in Communities and the Cardiovascular Health Study. The subjects were followed for 7 years. First VTE rate was 1.92 out of 1000. The condition was more prevalent among men and its occurrence increased with age. The annual recurrence rate during the 2-year period after the first VTE was 7.7 and the only reason for the disease recurrence was cancer (RR 9.2, 95% CI 2.0-41.7).[12]

In a cohort study, Hansson et al. followed 738 patients with DVT for 3.7-8.8 years and found the cumulative incidence of recurrent VTE to be 21.5% in 5 years. Their multivariate survival analysis revealed proximal DVT, cancer and previous history of thromboembolism to be independent risk factors for the VTE recurrence. They did not find any significant relations between age, sex, antithrombotic treatment or immobilization and disease recurrence.[19] In another study, White et al. followed 37000 patients with DVT for 6 months and suggested that DVT recurrence is related with age, cancer, surgeries and hospitalization duration.[18]

A clinical trial conducted by Schulman et al. followed 897 subjects, divided into two groups receiving vitamin antagonist for 6 weeks and 6 months for ten years, respectively. Regardless of the intervention group, disease recurrence was seen in 29.1% of all patients. This study found a significant association between disease recurrence and high age, being male, persistent risk factors especially venous insufficiency at baseline, proximal DVT, pulmonary embolism, and symptoms of impaired venous circulation disorder at the time of release.[25]

In 2005, Partsch reviewed the studies on acute DVT recurrence and reported that some studies suggested immobilization or restricted physical activity as important factors in disease recurrence. In addition, the same studies recommended walking accompanied with an appropriate compression on the involved site during the treatment period. His results indicated that immobilization, as one of Virchow's triad criteria, may cause venous stasis.[26] Prandoni et al. conducted a study on 377 DVT patients and found recurrent DVT associated with immobilization. Similar to Partsch inference, they also suggested quick mobilization of the patients and increasing their physical activity after the first DVT as a good treatment method.[3]

Several studies conducted on the relation between DVT recurrence and its associated risk factors including age, sex, cancer, bone fractures, hip and knee surgeries, proximal DVT, immobilization and coagulation disorders. However, these studies were most prospective and included patients with FDVT. Unlike the mentioned researches, our study did not find any significant relation between RDVT and cancer, age, surgery, sex, and proximal DVT. However, our results revealed the strong effect of immobilization on RDVT. In addition, numerous studies suggested coagulation disorders to be one of the most important factors causing DVT, either for the first time or as a recurrent disease. We could not prove coagulopathy as a risk factor. The reason might have been the care individuals with a history of disorders paid to their treatment. In other words, the concurrence of such disorders and a DVT incidence caused the patients to commit to treatment. Therefore, to our surprise, coagulopathy actually appeared as a preventive factor. A further prospective study would be beneficial in clearly understanding the issue.

The high rate of intravenous (IV) drug abusers (8.3%) among the patients in the present study was also noticeable. Previous studies on drug addicts suggested DVT as a complication caused by drug abuse (especially IV drug abuse). Mohammadzadeh et

al. studied 50 IV drug abusers in Northern Iran and indicated pseudo aneurysm with a frequency of 52% as the most common vascular complication among these subjects. DVT was the next common complication with a frequency of 18%.[27] Yegane et al. studied the effect of surgery on 62 IV drug abusers complaining from tenderness and swelling in the groin region and noted a high rate of DVT (50%) among these patients.[28]

In a case-control study, Masoomi et al. compared DVT patients with healthy subjects in central Iran (Kerman). They showed that in the regression model, the crude effect of opium addiction on DVT was very strong (OR 4.25, 95% CI 2.6-6.9). However, the effect was eliminated after multivariate regression analysis (OR 0.56, 95% CI 0.1-3).[29]

Based on the results from the present study, increased physical activity is recommended to individuals with long periods of immobilization. If the patient is able to move after the first DVT, they are suggested to start mobilization quickly and to be physically active during long haul flights. Moreover, considering the relationship between coagulation disorders and disease recurrence, an appropriate antithrombotic treatment would be necessary.

This was a retrospective study based on the information that patients provided for their physicians. A prospective study can follow the patients with first DVT and exactly record the risk factors and treatment methods applied to determine their effects on disease recurrence. Another point to keep in mind is to educate IV drug abusers about methods preventing thrombosis and the associated complications.

Conflict of Interests

Authors have no conflict of interests.

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