

Provoked venous thromboembolism during ten-year follow up at the Clinical Centre University of Sarajevo

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ABSTRACT

Aim To determine risk factors for deep vein thrombosis (DVT) in hospitalized patients in a 10-year follow-up.

Methods In this observational study data were collected from the disease history of patients admitted to the Department of Angiology of the Clinical Centre University of Sarajevo in the period of 10 years (2008-2017). Of 6246 hospitalized patients, 1154 were with established diagnosis of DVT and included in the study as a basic inclusion criterion.

Results Provoked venous thromboembolism was recorded in 45.75% of hospitalized patients. In 54.25% cases DVT was classified as idiopathic; in the remaining cases with DVT external risk factors were identified. Every fourth patient had a history of malignancy, and this risk factor was significantly more common among women and younger patients. Cancer of female reproductive organs, colon, lung, breast and prostate cancer were most common. One of 10 women had DVT during pregnancy or postpartum period. Out of the total number, 10.9% patients had DVT after surgery, 2.3% after injury. DVT was found in 1.6% of drug addicts. Rethrombosis was diagnosed in 5.2% patients within a year, while 9.2 % patients had rethrombosis within five years.

Conclusion Provoked venous thromboembolism is an entity that can be prevented. Malignancy and surgical treatment are the most common risk factors and these patients should be treated with special care. The creation of a register of patients with venous thromboembolism in Bosnia and Herzegovina would enable the development of a preventive strategy in the groups of patients at risk.

Key words: risk factors, thrombosis, treatment

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INTRODUCTION

Venous thromboembolism (VTE) includes two clinical entities, deep-vein thrombosis of the leg or pelvis and its complication, pulmonary embolism (PE) (1). Incidence of VTE in European population is about 104 to 183 per 100,000; it is predominantly a disease of older age, and an incidence rate after 45 years of age is generally higher in males (1). Diagnosis of DVT is difficult and unreliable. DVT often exists without clinical signs (without pain, temperature, and edema) which can be found in approximately 50% of patients (2). Provoked DVT is caused by a specific event (3). Thrombosis is caused by injury of the blood vessel i.e. endothelial dysfunction, by venous or circulatory stasis or hypercoagulable state (4,5). The most common causes are related to trauma, infections, surgical procedures and immobilization (4). Cardiovascular disease and cardiac failure, myeloproliferative diseases, malignant diseases, inflammatory bowel disease, severe systemic illness and iatrogenic vascular injury, previous venous thrombosis, excessive pulmonary embolism and chronic pulmonary hypertension are particularly significant risk factors (4,5). Another group of risk factors involve inherited risk factors, e.g. coagulation disorders, hereditary thrombophilia, genetic predisposition characterized by or disrupting anticoagulation potential or a disorder that induces a procoagulant state (4,5). The diagnosis is based on anamnestic data, clinical findings, analysis of coagulation parameters (non-specific) and D-dimer (negative D-dimer result excludes the existence of DVT while positive results indicate additional diagnostic methods) (6). Confirmation of the diagnosis is done by Colour Doppler (6).

Research will serve for better understanding of etiological factors for venous thromboembolism. In Bosnia and Herzegovina there have been no similar studies, and the data will be beneficial for clinicians in everyday clinical work.

The aim of this study is to determine risk factors for deep vein thrombosis in hospitalized patients in a 10-year follow-up in the Clinical Centre University of Sarajevo.

PATIENTS AND METHODS

Patients and study design

In this observational study data were collected from the disease history of patients admitted to the Department of Angiology of the Clinical Centre University of Sarajevo in the period of 10 years (2008-2017). Out of 6246 hospitalized patients in that period, 1154 (18.48%) with established diagnosis of DVT were included in the study as the basic inclusion criterion.

Data on individual risk factors, complications of baseline disease, as well as appearance of retrombosis were collected. Incomplete information in the history of the disease was the exclusive criterion for the study.

Methods

The diagnosis was confirmed by ultrasound VI-VID S5 with 12 L linear probe (General Electric, Boston, Massachusetts, United States) or Logiq Book XP with 8L curvilinear probe (General Electric, Boston, Massachusetts, United States) along with values of fibrinogen (reference value is 5.3-10.3 mmol/L) and D-dimer value (reference value is <0.55 µg/L).

Statistical analysis

The χ^2 test, Mann-U Whitney test, Pearson and Spearman's correlation were used for an analysis. χ^2 test of independence (with Yates's correction for continuity) was used to investigate the relationship between sex and frequency of risk factors (phi - measure of association between two binary variables).

The relationship between the age of the patient and the existence of provocative exogenous factor for DVT was investigated by the Pearson coefficient (r). The level of statistical significance for $p < 0.05$ was accepted. Preliminary analyses were carried out in order to confirm the assumptions about normality, linearity and homogeneity of the variance. The malignancy data did not meet the Pearson correlation criteria, so the Spearman correlation coefficient (ro) was calculated.

RESULTS

Of the total number of DVT patients (n=1154), 600 (51.99%) were females and 554 (48.01%) were males. A total of 528 (45.75%) patients were classified as provoked DVT because an exogenous risk factor for deep vein thrombosis was detected, of which a history of malignancy was the most represented one, 299 (56.6%).

According to the gender, history of malignancy and surgery within a few months before hospitalization due to DVT were the most presented risk factors in both females and males, 176 (out of 329; 53.5%) and 123 (out of 199; 61.8%), and 76 (23.1%) and 50 (25.1%), respectively.

Among 329 female patients 58 (17.6%) had DVT in pregnancy or in the postpartum period (Table 1).

Table 1. Risk factors for deep venous thrombosis (DVT)

Risk factor	No (%) of patients			p	phi
	Females	Males	Total		
Malignancy	176 (53.4)	123 (61.8)	299 (56.6)	0.008	-0.08
Drug abuse	5 (1.5)	14 (7.0)	19 (3.5)	0.043	0.06
Pregnancy	58 (17.6)	0	58 (10.9)	/	/
Surgery	76 (23.1)	50 (25.1)	126 (23.8)	0.059	-0.05
Injury	14 (4.2)	12 (6)	26 (4.9)	1.0	-0.006
Total	329 (62.3)	199 (37.7)	528 (100)		

Phi, association between two binary variables

An analysis of relationship between gender and frequency of risk factors showed that provoked DVT was more common in females than in males (p <0.005; phi = -0.14). Prevalence of malignancy in females was statistically significantly higher compared to males (p=0.008) Prevalence of drug addiction was statistically significantly higher in males comparing to females, 14 (7.0%) and five (1.5%), respectively (p=0.043) (Table 1).

An analysis of relationship between patients' age and provocative exogenous factor for DVT showed reduced prevalence of provoked DVT in older patients (r = -0.093; p=0.002).

The most common malignancy in women was cancer of female reproductive organs, which was presented in 58 (out of 176; 32.95%) (1/3 of all malignancies in women, or in almost every ten among 600 women with DVT (58/600; 9.67%). In male patients prostate and testicular cancer were the most common, in 27 (out of 123; 21.95%) patients, i.e. every twelfth man had prostate or testicular cancer (4.87% out of 554 males with DVT); it was similar to colon cancer, 24 (out of 123;

Table 2. Age correlation with risk factor for deep venous thrombosis (DVT)

Risk factor	r/ro	p	Explanation
Malignancy	-0.138	0.018	Small negative correlation - rare malignancy preceded DVT in older patients
Drug abuse	-0.202	<0.0005	Small negative correlation - less narcotics preceded DVT in older patients
Pregnancy	-0.379	<0.0005	Medium negative correlation - rare pregnancy DVT in older patients
Surgery	0.007	0.818	Small positive correlation - more frequent surgery preceded DVT in elderly patients
Injury	0.015	0.616	Small positive correlation - more frequent injury was preceded by DVT in elderly patients

r/ro - correlation between risk factor and patient age

Table 3. Malignancy among patients with deep venous thrombosis

Malignity	No (%) of patients		
	Females	Males	Total
Cancer of female reproductive organs	58 (100)	0	58 (19.4)
Colon cancer	22 (47.8)	24 (52.2)	46 (15.4)
Lung cancer	16 (50)	16 (50)	32 (10.7)
Breast cancer	28 (100)	0	28 (9.4)
Prostate cancer	0	23 (100)	23 (7.7)
Cancer of the urinary tract	6 (31.6)	13 (68.4)	19 (6.35)
Pancreas cancer	5 (27.7)	13 (72.3)	18 (6)
Leukaemia / lymphoma	10 (62.5)	6 (37.5)	16 (5.35)
Brain tumour	7 (50)	7 (50)	14 (4.7)
Stomach cancer	6 (66.6)	3 (33.4)	9 (3)
Abdominal tumour	7 (87.5)	1 (12.5)	8 (2.6)
Cancer of the biliary tract	5 (83.3)	1 (16.7)	6 (2.0)
Unknown primary focus	1 (25)	3 (75)	4 (1.3)
Larynx cancer	0	3 (100)	3 (1)
Melanoma	0	3 (100)	3 (1)
Testicular cancer	0	3 (100)	3 (1)
Pelvic cancer	1 (50)	1 (50)	2 (0.6)
Thyroid gland cancer	1 (50)	1 (50)	2 (0.6)
Parathyroid gland cancer	0	1 (100)	1 (0.3)
Pharynx cancer	1 (100)	0	1 (0.3)
Suprarenal gland cancer	1 (100)	0	1 (0.3)
Liver cancer	0	1 (100)	1 (0.3)
Mesothelioma	1 (100)	0	1 (0.3)
Total	176 (58.8)	123 (41.2)	299 (100)

19.51% of all malignancies (4.33% of all males with DVT). No statistically significant difference in presentation of individual malignancies was found between the genders (Table 3).

A recurrence of deep venous thrombosis was diagnosed in 175 (15.1% of 1154 patients diagnosed with DVT) patients. The majority of patients, 154 (out of 1154 patients; 13.3%) were treated for the first time diagnosed rethrombosis, while 15 (out of 1154 patients; 1.3%) of cases were treated for the second rethrombosis. In six (out of 1154; 0.5%) patients three or more recurrences were noticed,

while 60 (out of 1154; 5.2%) patients had a rethrombosis within a year and 106 (9.2%) patients had a rethrombosis within five years. The average time between the previous and the current rethrombosis was 5 years, ranging from rethrombosis during hospitalization (seen in nine patients) to rethrombosis 50 years later. No significant difference in the occurrence of rethrombosis and in the time period between the episodes of DVT in males compared to females was found ($p=0.78$; $\phi=0.10$, and $p = 0.39$; $z = -0.84$, respectively).

DISCUSSION

The clear exogenous risk factor venous thromboembolism was detected in 45.75% of our patients and DVT was identified as provoked, which is less in the comparison to the previous studies (7). A number of risk factors for DVT has been identified and now it is widely accepted that many of these factors can act (1). Every fourth patient in our study had a cause in malignancy. Malignancy has long been recognized as a risk factor for DVT, which is explained by multiple pathophysiological mechanisms including direct hormonal tumour effects, surgical treatment, chemotherapy, immobilization (1). Cancers of female and male reproductive organs, colon, lungs and breast were the most common among our hospitalized patients with DVT, which somewhat corresponds to literature data where, as the most common types of tumours found in patients with lungs, colon, breast and prostate cancer (2); it could be explained by the high prevalence of these malignancies in general population in the world (1). On the other hand, it is stated that oncology patients, those with ovarian, brain and pancreatic cancer have the highest incidence of VTE, while those with head and neck cancer, the bladder and breast have the least risk (8). Pregnant women have about 4 times the risk of venous thromboembolism compared to non-pregnant reproductive women (9); in our study 1 out of 10 women had DVT in pregnancy or postpartum period. This risk starts already in the first trimester of pregnancy (9). Pregnancy increases the risk of DVT due to the combination of immobilisation, venereal and in oculum vein cavity compression, hormonal effects and hypercoagulability (9).

Our results of risk factors analysis are comparable with the results of a similar study in the United States that included 885 patients with DVT over a 10-year period (10): in 25.9% of our patients malignancy was found, which is considerably more than 10% of patients in the US study. In most of other studies oncology patients account for 15-20% of all cases of venous thromboembolism (11). On the other hand, only 10.9% of our patients had DVT that could be associated with surgery, while in the US study, as many as 35% of patients had a postoperative incident (10). Prolonged surgery or lack of thromboprophylaxis in particular increase this risk; the literature suggests that the postoperative risk is greatest for abdominal cancer, hip replacement, or neurosurgery with deficiencies (12). Injuries, as a risk factor, are also less represented in our results. In up to 50% of patients with venous thrombosis, hereditary prothrombotic disorders (genetic mutations with loss of antithrombin III, protein C, or protein S function, or with the enhancement of factor V Leiden or prothrombin) can be identified (13). Rethrombosis showed up in 5.2% and 9.2% of our patients within a year and five years, respectively, which is considerably lower than shown in other studies, 7% and 21.5%, respectively (14). It could be explained by the fact that high percentage of thromboses rests undiagnosed, and that it is possible that the recurrence was treated in another health institution. The risk of rethrombosis is higher among patients whose first episode of DVT is associated with malignancy, and the smallest among patients whose first episode is associated with transient risk factors such as surgery (15). One study indicates a 60% higher risk of relapse in males compared to females (16). In our study, rethrombosis was more common in males.

In conclusion, it is recommended to create a register of patients with venous thromboembolism in Bosnia and Herzegovina, which would enable the development of a preventive strategy in the patient risk groups.

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TRANSPARENCY DECLARATION

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