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Original Research Article

Factors that influence deep vein thrombosis of lower limbs in stroke patients, and the effect of anticoagulant intervention

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Abstract

Purpose: *To evaluate the factors influencing deep vein thrombosis (DVT) in stroke patients, and the effect of anticoagulant intervention.*
Methods: *A total of 208 stroke patients in Jiaozhou Central Hospital of Qingdao from March 2018 to March 2020 were assigned to DVT group (n = 84) and non-DVT group (n = 124). Their clinical data were analyzed to identify risk factors. Thereafter, the DVT group were randomized to control group and study group (n = 42 each). Conventional treatment and low molecular heparin plus treatment were given to the groups, respectively. Activities of daily living (ADL) and treatment outcomes were compared.*
Results: *Univariate analysis showed that age, smoking history, Wells score, duration of bed rest, limb immobilization time after interventional therapy, D-dimer and TGs differed between the two groups ($p < 0.05$). Multivariate logistic regression analysis revealed that age ≥ 60 years old, smoking history, Wells score ≥ 2 points, duration of bed-rest ≥ 7 days, limb immobilization time ≥ 1 day after intervention, D-dimer < 0.95 mg/L and TG < 1.84 mmol/L were risk factors for DVT. After treatment, ADL and total treatment effectiveness in the study group were higher than in the control group ($p < 0.05$).*
Conclusion: *Age ≥ 60 years, smoking history, Wells score ≥ 2 points, duration of bedrest ≥ 7 days, limb immobilization time ≥ 1 day after intervention, D-dimer < 0.95 mg/L and TG < 1.84 mmol/L are risk factors for DVT. The anticoagulant used (rivaroxaban) seems to improve daily living and reduce clinical symptoms.*

Keywords: *Stroke, Deep vein thrombosis, Anticoagulants, Intervention effect*

INTRODUCTION

In recent years, the incidence of stroke has been on the rise in China, and it is characterized by high disability and mortality [1]. One of the common complications of stroke is deep vein thrombosis (DVT) of the lower extremities which ranks third in severity after coronary artery disease and cerebrovascular disease [2]. Deep vein thrombosis (DVT) is caused by blood coagulation or blood retention in the deep veins of the lower extremities. This results in vascular occlusion, stenosis, and slow blood circulation, leading to a series of symptoms such as deep vein pain, swelling and pigmentation in the lower extremities [3]. Studies have suggested that stroke patients are a high-risk group for DVT, with 5 - 40% probability of DVT after stroke, which poses threats to the health and quality of life of patients [4]. Therefore, it is essential in modern medicine to carry out early diagnosis of the disease, determine factors that influence lower extremity DVT, and to carry out interventions to prevent or reduce the risk of death as a result of the disease.

Currently, anticoagulant drugs are frequently used for the treatment of stroke patients with DVT in the lower limbs. The anticoagulants produce remarkable outcomes by dissolving thrombus [5,6]. However, to date, there are no studies on factors that influence stroke with lower limb DVT in patients, as well as the effect of anticoagulant intervention. Therefore, this study was aimed at identifying factors that influence lower extremity DVT in stroke patients, using 208 stroke patients diagnosed and confirmed in Jiaozhou Central Hospital of Qingdao from March 2018 to March 2020.

METHODS

Subjects

A total of 205 stroke patients diagnosed and confirmed in our hospital from March 2018 to March 2020 were recruited. The patients comprised 165 males and 95 females aged 22 - 76 years (mean age = 57.4 ± 12.7 years).

Inclusion/exclusion criteria

Inclusion criteria

The following categories of patients were included in this study: (a) patients who met the diagnostic criteria for stroke [7], and patients diagnosed for stroke using Computerized Tomography (CT), CT angiography (CTA), and Magnetic Resonance Imaging (MRI); (b) patients with complete clinical data; (c) stroke patients aged ≥ 18 years; (d) patients admitted within 72 h of onset of stroke, and (e) patients with no history of allergy or contraindications to anticoagulant drugs.

Exclusion criteria

The following categories of patients were excluded: (a) patients with unstable vital signs or critical illness requiring ventilator; (b) those with a history of stroke; (c) pregnant or lactating patients; (d) patients with brain tumor; (e) patients who received radiotherapy or chemotherapy within the previous six months; (f) patients who had severe diseases in other organs e.g. liver, lung, kidney and other vital organs; (g) patients who refused to cooperate during the study, and those who were lost during follow-up, as well as patients who withdraw halfway into the research. The patients were divided into DVT group (n = 84) and non-DVT group (n = 124), based on whether or not they had complication with DVT at the lower extremities. Patients in the DVT group were randomly assigned to a study group and a control group, each with 42 patients. The protocol involved in this study was reviewed and approved by the Medical Ethics Committee of Jiaozhou Central Hospital of Qingdao hospital (approved no. 2018LC34-124), and each patient provided a signed consent form. The srudy followed the international guidelines for human studies [8].

Clinical profile of patients

The medical records of the stroke patients were retrieved electronically to access clinical information on gender, age, body mass index (BMI), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking history (average number of cigarettes > 1/day, and duration of smoking ≥ 1 year); level of alcohol intake (average daily ethanol intake > 50 ml); history of hypertension and diabetes, infection, Glasgow Coma Scale (GCS) score, Wells score (scores <2 indicated low possibility of pulmonary embolism, while scores ≥ 2 points indicated medium or high possibility of embolism); femoral vein puncture, varicose veins, lower extremity vascular stenosis and duration of bedrest. Other clinical information retrieved were limb immobilization time, and laboratory test indicators after interventional treatment [albumin, D-dimer, homocysteine (Hcy), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triacylglycerol (TG), procalcitonin (PCT), thrombin time (TT), prothrombin time (PT), and activated partial thromboplastin time (APTT)].

Treatments

The control group received conventional treatment for enhancement of blood circulation and removal of blood stasis, as well as anti-platelet aggregation therapy using oral enteric-coated aspirin tablets (China Shijiazhuang

Pharmaceutical Group Ouyi Pharmaceutical Co. Ltd., National Medicine Standard: H13023635), 100 mg once/day), and Clopidogrel (Sanofi Winthro Industrie, National Medicine Standard: J20130083) 75 mg/day. Patients in the study group received subcutaneous injection of low molecular heparin close to the umbilical area, at a dose of 200 U/kg body weight per day, 2 times/day, along with orally-administered warfarin sodium tablets (Shanghai Xinyi Pharmaceutical Co. Ltd., National Medicine Standard H31022123). The first dose of warfarin was 5.00 mg once daily, while the later dose was 2.5 mg/day. Patients in both groups were treated for 6 months, and they were followed up for 6 months after treatment.

Evaluation of treatment efficacy

Risk factors for lower extremity DVT were determined. Activity of Daily Living (ADL), and clinical treatment efficiency in the two groups before and after treatment were also measured and compared. The standard for evaluation of ADL [9] was applied to determine the ability of patients to take care of themselves daily. There were ten items in the ADL standard, and it adopted a 4-level scoring method based on the following: *complete dependence*, *need for considerable help*, *partial need for help/partial independence* and *total independence*. The scores ranged from 0 to 15 points. Higher total scores indicated better ability of the patient to cope with daily living. Treatment effectiveness was assessed using color Doppler ultrasound for checking blood vessel diameter and wall thickness, before and after treatment, to determine the presence of echo as well as blood flow signals [10]. Total effectiveness was scored as follows: treatment was classified as *significantly effective* if after anticoagulant treatment, swelling of the affected limb was significantly reduced, circumference of each lower limb was ≤ 1 cm (which was basically the same as that of healthy limb), and most of the thrombi were dissolved without blood vessel blockage. Treatment was classified as *effective* if the swelling in the patient's affected limb was reduced, with little difference in the circumference of the lower limbs, and partial dissolution of the thrombi. On the other hand, treatment was deemed *ineffective* if there was no significant improvement in the swelling of the patient's affected limb, or if the symptoms became worse. Total effectiveness rate (TER) was calculated as in Eq 1.

TER (%) = {(Nse+Ne)/Nt}100 .... (1)

Where Nse=no. of the significantly effective cases, Ne= no. of the effective cases, Nt= total no. of cases.

Statistical analysis

Measurement data are expressed as mean ± standard deviation (SD), and *t*-test was used for comparison between groups. Count data are expressed as %, and were compared using χ^2 test. Univariate analysis and logistic regression analysis were used to determine the risk factors for lower extremity DVT following stroke. Differences with statistical significance were assumed at *p* values less than 0.05. All statistical analyses were carried out using SPSS software (version 25, SPSS, Inc., Chicago, IL, USA).

RESULTS

Univariate analysis data for patients with stroke and DVT in lower limbs

Results from univariate analysis showed no statistically significant differences in gender, BMI, HR, SBP, DBP, history of drinking alcohol, history of hypertension, history of diabetes, infection, GCS score, femoral vein puncture, varicose veins, degree of lower limb vascular stenosis, as well as levels of albumin, Hcy, LDL-C, HDL-C, TC, PCT, TT, PT and APTT between the two groups (p>0.05). However, significant differences between the two groups were observed in age, smoking history, Wells score, duration of bedrest, interventional treatment, limb immobilization time, D-dimer and TG ($p < 0.05$). These results are shown in Table 1~3.

Risk factors for lower limb DVT in stroke patients

Factors with statistical differences based on univariate analysis (age, smoking history, Wells score, bed time, limb immobilization time after interventional treatment, D-dimer and TG) were taken as independent variables, while factors for DVT of the lower limbs (yes = 1, no = 0) were taken as dependent variables, as shown in Table 4. Multivariate logistic regression analysis revealed that age ≥ 60 years old, smoking history, Wells score ≥ 2 points, duration of bed rest ≥ 7 days, limb immobilization time ≥ 1 day after interventional therapy, D-dimer <0.95 mg/L and TG < 1.84 mmol/L were risk factors for lower limb DVT in stroke patients ($p < 0.05$). These results are presented in Table 5.

Table 1: Univariate analysis in the general data for stroke patients with lower limb DVT

Factor	DVT group (n=84)	Non-DVT group (n=124)	t/χ2	*P*-value
Gender (Male/Female)	49/35	74/50	0.037	0.847
Age (< 60/≥60)	30/54	66/58	6.179	0.013
BMI (≥25/＜25)	47/37	71/53	0.035	0.852
HR (times/min)	92.55±19.65	91.89±20.04	0.235	0.814
SBP (mmHg)	121.74±20.63	123.35±19.88	0.564	0.573
DBP (mmHg)	73.56±14.35	74.32±12.45	0.406	0.685
Smoking history (Yes/No)	46/38	38/86	12.089	0.001
Drinking history (Yes/No)	43/41	56/68	0.730	0.393
hypertension (Yes/No)	39/45	69/55	1.704	0.192
Diabetes (Yes/No)	45/39	70/54	0.168	0.682
Infections (Yes/No)	38/46	50/74	0.496	0.481

Table 2: Univariate analysis in the Treatment-related factors of stroke patients with lower limb DVT

Factor	DVT group(n=84)	Non-DVT group(n=124)	t/χ2	*P*-value
GCS score (6~8/<6)	44/40	53/71	1.870	0.172
Wells score (<2/≥2)	24/60	79/45	24.734	<0.001
Femoral venous puncture (Yes/No)	43/41	66/58	0.083	0.773
Varicosity (Yes/No)	18/66	22/102	0.438	0.508
Lower limbs stenosis (%)			0.016	0.899
<50	67(40.61)	98(59.39)		
≥50	17(39.53)	26(60.47)		
Duration of bed rest(days)			15.088	<0.001
<7	16(22.22)	56(77.78)		
≥7	68(50.00)	68(50.00)		
Immobilization time after interventional treatment(days)			11.331	0.001
<1	23(26.74)	63(73.26)		
≥1	61(50.00)	61(50.00)		

Table 3: Univariate analysis in the serum factors of stroke patients with lower limb DVT

Factor	DVT group (n=84)	Non-DVT group(n=124)	t/χ2	*P*-value
Albumin (g/L)	40.77±5.38	42.77±5.75	1.616	0.107
D-dimer(mg/L)	1.68±0.52	0.89±0.24	14.770	<0.001
Hcy(μmol/L)	17.97±4.75	19.05±5.01	1.558	0.121
LDL-C (mmol/L)	2.59±0.82	2.52±0.78	0.622	0.535
HDL-C (mol /L)	1.23±0.40	1.15±0.30	1.647	0.101
TC (mmol/L)	4.18±0.90	4.35±1.19	1.111	0.268
TG (mmol/L)	2.45±0.33	1.58±0.59	10.860	<0.001
PCT (ng/mL)	0.60±0.15	0.56±0.17	1.745	0.083
TT (sec)	18.22±5.55	18.66±5.71	0.552	0.582
PT (sec)	13.26±3.44	13.66±3.56	0.806	0.421
APTT (sec)	34.13±6.86	33.96±6.85	0.176	0.861

Table 4: Analysis of risk factors for lower limb DVT in stroke patients, and assignments

Factor	Code	Assignment
Age	X1	0=＜60 years, 1= ≥60 years
History of smoking	X2	0=no, 1=yes
Wells score	X3	0=＜2 points, 1=≥2 points
Duration of bed rest	X4	0=＜7 days, 1=≥7 days
Immobilization time after interventional treatment	X5	0=＜1d, 1=≥1 day
D-dimer	X6	0=≥0.95mg/L, 1=＜0.95mg/L
TG	X7	0=≥1.84mmol/L, 1=＜1.84mmol/L

Table 5: Logistic regression analysis of multiple factors that may affect lower extremity DVT in stroke patients

Factor	B	SE	Wald χ^2	*P*	OR	95% CI
Age ≥ 60 years	0.717	0.265	5.640	0.009	2.048	1.004～4.614
History of smoking	1.007	0.230	5.097	0.010	2.738	1.511～6.522
Wells score ≥2 points	1.478	0.257	9.472	＜0.001	4.386	2.782～8.236
Duration of bedrest ≥7 days	1.641	0.223	4.837	0.018	5.158	3.116～9.043
Immobilization time after interventional treatment ≥1 day	1.008	0.346	7.640	＜0.001	2.740	1.082～5.635
D-dimer < 0.95 (mg/L)	1.389	0.367	6.329	＜0.001	4.012	3.082～7.606
TG < 1.84 (mmol/L)	1.637	0.221	8.231	＜0.001	5.142	3.082～8.030

ADL of patients before and after intervention

Table 6 shows that prior to intervention, there was no statistically significant difference in ADL between the two groups of patients ($p > 0.05$). However, after intervention, the ADL of both groups increased significantly, but the study group had a much higher level of ADL than the control group ($p < 0.05$).

Table 6: Comparison of the ability of daily living of the two groups of patients before and after intervention (points, mean ± SD)

Group	Before intervention	After intervention
Study (n=42)	62.38±11.03	90.31±12.36
Control (n=42)	62.40±10.98	79.36±11.45
T	0.008	4.212
P-value	0.993	<0.001

Treatment effectiveness

As shown in Table 7, treatment effectiveness was markedly higher in the study group than in the control group (97.62 vs 80.95 %) ($p < 0.05$).

DISCUSSION

One of the serious complications of stroke seen frequently in clinics is DVT of the lower limbs. Due to symptoms such as weakness, paralysis and impairment of consciousness, stroke patients need to stay in bed for a long time. Therefore, they are prone to venous stasis which promotes platelet aggregation, which further exacerbates venous stasis, resulting in a hypercoagulable state. Venous stasis causes damage to the vascular intima, thereby leading to DVT [11].

Numerous trials have demonstrated that about 20% of stroke patients may develop DVT, and the incidence of DVT among stroke has been on the increase yearly, especially in recent years. Therefore, there is need to screen stroke patients and implement interventional treatments so as to reduce the risk of DVT in the lower limbs following stroke.

The present study showed that lower extremity DVT occurred in 84 of the 208 stroke patients (40.38%), indicating that stroke patients are a high-risk group for lower extremity DVT. It is important to note that gender, BMI, HR, SBP, DBP, history of alcohol intake, history of hypertension, history of diabetes, infections, GCS score, femoral vein puncture, varicose veins, lower limb vascular stenosis, and levels of albumin, Hcy, LDL-C, HDL-C, TC, PCT, TT, PT and APTT did not differ significantly between the study and control groups. However, there were significant differences between the two groups, with respect to the age, smoking history, Wells score, and duration of bedrest, limb immobilization time, and levels of D-dimer and TG after interventional treatment.

Table 7: Comparison of effectiveness of clinical treatment between the two groups of patients {n (%)}

Group	Markedly effective	Effective	Ineffective	Total effectiveness
Study (n=42)	29 (69.05)	12 (28.57)	1 (2.38)	41 (97.62)
Control (n=42)	19 (45.24)	15 (35.71)	8 (19.05)	34 (80.95)
χ^2				6.098
P-value				0.014

Multivariate logistic regression demonstrated that age ≥ 60 years old, smoking history, Wells score ≥ 2 points, duration of bed rest ≥ 7 days, limb immobilization time ≥ 1 day after interventional therapy, D-dimer <0.95 mg/L and TG < 1.84 mmol/L were risk factors for lower extremity DVT in stroke patients. These findings may be due to the fact that old age is often accompanied by a variety of chronic diseases, coupled with poor physical condition, decreased exercise, poor physical fitness, poor blood vessel elasticity and high activities of blood coagulation factors which slow down venous blood circulation in the lower limbs. Moreover, local oxygen supply to the venous valves is insufficient, leading to venous endothelial lesions. In addition, studies have shown that the consumption of inhibitors of coagulation factors, and the accumulation of local coagulation factors increase the risk of intravenous thrombosis [15].

The results may also be explained by the fact that the particulate matter and gas produced by smoking inhibit the synthesis of apolipoprotein (Apo) via oxidative stress, leading to abnormal lipid metabolism [16], aggravated vascular stenosis, and increased risk of deep venous atherosclerosis of the lower limbs. Wells is a clinically used diagnostic index for prediction of DVT in the lower extremities. Studies have shown [17] that Wells score ≥ 2 is an independent risk factor for DVT after stroke, suggesting that the higher the Wells score, the higher the risk of lower extremity DVT in stroke patients [17]. Similar results were obtained in this study.

Patients with long-term bedrest and excessive limb immobilization after interventional therapy are prone to slow blood flow and stasis, and blood flow stasis promotes platelet aggregation, resulting in decreased rate of blood flow, hypercoagulable state of blood, and impaired endangium, which in turn accelerate the complications of lower limb DVT following stroke. In a previous trial, it was revealed that under normal circumstances, when people travel in cars, trains and airplanes for ≥8 h, the incidence of DVT might increase up to 4 % [18]. The longer the immobilizations time after interventional treatment, the higher the risk of DVT following stroke. Serum D-dimer is an activation product of thrombin and plasmin. An increase in serum D-dimer level indicates an increase in the degradation products of plasmin which are sensitive markers of thrombosis, and also independent risk factors for patients with lower limb DVT after stroke [19]. It is known that TG is a risk factor for diabetes and stroke [20]. High levels of blood sugar and blood lipids lead to changes in vascular function and long-term disorders in lipid metabolism, resulting in decreased vascular endothelial and diastolic function, and ultimately DVT.

The use of anticoagulant drugs is currently the most popular treatment strategy for deep vein thrombosis in patients with stroke. The anticoagulant drugs used in clinics are dabigatran, rivaroxaban, warfarin and low-molecular weight heparin. Low-molecular-weight heparin is derived from unfractionated heparin through chemical depolymerization and enzymatic treatment. Low-molecular-weight heparin exerts a strong anti-Xa effect, and it has high half-life and high bioavailability. It binds less to plasma proteins, increases the activities of anticoagulants, and prevents the production of thromboxane [21].

Studies have shown that when low-molecular-weight heparin was subcutaneous injected, it was bound to antithrombin, thereby exerting an anticoagulant effect [22]. Warfarin is a moderately effective anticoagulant, and its mechanism of action is to reduce the aggregation of platelets by inhibiting the activity of thrombin, thereby acting as an anti-platelet aggregation. The drug is used mainly for patients who need long-term anticoagulation to suppress thrombosis. The present study has demonstrated that after treatment, the activity of daily living in the two groups of patients increased significantly, but it was higher in the study group than in the control group. Moreover, total effectiveness of treatment in the study group (97.62%) was markedly higher than the corresponding value in the control group (80.95%). Thus, the use of rivaroxaban for anticoagulation therapy resulted in a satisfactory outcome.

CONCLUSION

Age ≥ 60 years, smoking history, Wells score ≥ 2 points, duration of bed rest ≥ 7 days, limb immobilization time ≥ 1 day after interventional therapy, D-dimer <0.95 mg/L and TG <1.84 mmol/L are risk factors for lower limb DVT in stroke patients. The use of an anticoagulant drug, such as rivaroxaban, reduces the symptoms of the disease and improves the patient's ability to cope with daily living.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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