Incidence and Risk Factors of Deep Vein Thrombosis with Complex Regional Pain Syndrome in Neurological Patients

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Abstract

Background and Objective: Deep vein thrombosis is most common in immobilized patients. Patient with neurological disorders often experienced weakness and swelling in one or both legs with possibility of deep vein thrombosis. Some patients experienced swelling and pain from complex regional pain syndrome, which is sometimes not distinguished by clinical symptoms alone. The aim of this research is to determine the incidence, risk factor and the difference of clinical symptoms affecting leg swelling due to deep vein thrombosis associated with localized complex pain syndrome in neurological disorder patients with unilateral leg edema.

Methods: In this retrospective cohort study, we examined the clinical and imaging data of unilateral leg edema patients from medical records. Patients were tested for deep vein thrombosis by venous doppler ultrasound and documented complex regional pain syndrome by using Budapest clinical criteria. Multiple logistic regression analysis included relevant confounders and potential predictors was performed.

Results: In univariate analysis, malignancy (p=0.042; OR,1.52; 95%CI,1.04-1.74), cerebrovascular disease (p<0.001; OR,2.17; 95%CI,1.49-4.01), spinal cord disease (p=0.021; OR,0.79; 95%CI,0.61-0.96), complex regional pain syndrome (p<0.001; OR,4.25; 95%CI,1.99-6.43) and nerve root surgery (p=0.034; OR,1.54; 95%CI,1.02-3.43) associated with deep vein thrombosis. Complex regional pain syndrome (p<0.001; OR,3.46; 95%CI,2.02-6.95) and cerebrovascular disease (p<0.001; OR,2.13; 95%CI,1.05-3.49), were a significant predictor of deep vein thrombosis in the final multivariate logistic regression model.

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Conclusion: Complex regional pain syndrome might be a precipitate cause of deep vein thrombosis in neurological disorder patients due to interrelated inflammation-thrombosis mechanism.

Keywords: chronic regional pain syndrome, deep vein thrombosis, leg edema

Introduction

Patients with neurological disease was found that some of these patients had leg swelling and pain. Differential diagnosis in these patients with leg swelling is important. This is because treatment approaches are different and could affect other serious complications, such as acute pulmonary embolism from deep vein thrombosis. Deep vein thrombosis is most common in immobilized patients, especially in the leg and in the recovery period. Patients with neurological disorders often experienced weakness in one or both legs[1-3], and caused swelling of the legs and the possibility of deep vein thrombosis. Some patients experienced swelling and pain from complex regional pain syndrome, which could not distinguish by clinical symptoms alone. While the exact incidence is not clearly known.[4-6] Although these two conditions shared some risk factors, such as surgery, leg weakness, but the relationship between these two conditions is not clearly known.[7-9] The aim of this research is to determine the incidence, risk factor and the association of deep vein thrombosis and complex regional pain syndrome in neurological disorder patients with leg edema.

Materials and Methods

Study population

This study is retrospective cohort study of unilateral leg edema patients in Neurological institute of Thailand between January 2559-December 2563. We retrospectively examined the clinical and risk factors of unilateral edema patients from medical records. We collected demographic data and clinical risk factors such as age, sex, history of malignancy or active cancer, history of cerebrovascular disease, history of spinal cord disease, history of nerve root disease, history of paralysis or paresis, type of surgery, D-dimer level.

Definitions

Unilateral leg edema was defined as patient who detected leg swelling by measuring in the mid-thigh circumference or mid-calf circumference, with a circumference of at least 3 cm greater than the other leg.

Deep vein thrombosis was defined as clinical symptoms, signs and results of the doppler ultrasound examination.

Complex regional pain syndrome was defined as clinical symptoms and signs depending on Budapest criteria[10]

1. Continuous pain disproportionate to the event that caused it
2. Symptoms (must meet at least one symptom in three of the four categories) Sensory: hyperesthesia and/or allodynia Vasomotor: asymmetry in skin temperature and/or asymmetry of skin colour and/or changes in skin colour Sudomotor: edema and/or sweating changes and/or asymmetric sweating Motor: decreased range of motion and/or motor dysfunction (tremor, dystonia, weakness) and/or trophic changes (skin, hair, nails)
3. Signs (must meet at least one sign in two or more of the four categories) Sensory: evidence of hyperalgesia (to puncture) and/or allodynia (touch/temperature/deep pressure/joint movement) Vasomotor: asymmetry in skin temperature >1 °C and/or asymmetry of skin colour and/or changes in skin colour Sudomotor: evidence of edema and/or sweating changes and/or asymmetric sweating Motor: evidence of decreased range of motion and/or motor dysfunction (tremor, dystonia, weakness) and/or trophic changes (skin, hair, nails)
4. Rule out other conditions that may explain the previous symptoms and signs.

Statistical Analysis

Sample size calculation

By using data from previous study[11,12], by substituting P1=0.069, P2=0.168, and the proportion of both populations (r)=2, sample size by using continuity correction=435 people was obtained. Sample size calculation based on following formula.[13]

$$n_{exposure} = \left[\frac{z_{1-\frac{\alpha}{2}} \sqrt{\bar{p}\bar{q}\left(1+\frac{1}{r}\right)} + z_{1-\beta} \sqrt{p_1 q_1 + \frac{p_2 q_2}{r}}}{\Delta} \right]^2$$

$$p_1 = P(outcome|exposure), q_1 = 1 - p_1$$

$$p_2 = P(outcome|unexposure), q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + p_2 r}{1+r}, \bar{q} = 1 - \bar{p}, r = \frac{n_{unexposure}}{n_{exposure}}$$

Continuous variables were presented as the mean. Categorical variables were described as percentages. The difference in baseline characteristic were analyzed using t test for continuous variables and the chi-square test for categorical variables.

Multiple logistic regression analyses were used to identify the risk factors of unilateral leg edema. The predictor variable included in multiple logistic regression model were malignancy, cerebrovascular disease, spinal cord disease, complex regional pain syndrome, nerve root surgery. Odd ratios and 95% confidence interval were used to illustrate the association.

The level of significance was set at a value of P less than 0.05. All statistical analyses were performed using SPSS for windows version 16.0 (IBM, Armonk, NY).

Results

Baseline characteristic of this study are summarized in Table1. A total of 480 unilateral leg edema patients (245 men, 235 women) with mean age 68.2 years were included in this study. All of patients had neurological disorders such as malignancy in nervous system, cerebrovascular disease, spinal cord disease or nerve root disease. Incidence of deep vein thrombosis was 22.1 case/person-year and incidence of complex regional pain syndrome was 9.7 case/person-year. The proportion of malignancy, cerebrovascular disease, spinal cord disease and nerve root disease were 17.7%, 23.1%, 24.3%, 34.8% respectively. The average mean of D- dimer level was 875.0 microgram per liter in deep vein thrombosis group and 934.5 microgram per liter in no deep vein thrombosis group respectively. In univariate analysis, malignancy (p=0.042; OR,1.52; 95%CI,1.04-1.74), cerebrovascular disease (p<0.001; OR,2.17; 95%CI,1.49-4.01), spinal cord disease (p=0.021; OR,0.79; 95%CI,0.61-0.96), complex regional pain syndrome (p<0.001; OR,4.25; 95%CI,1.99-6.43) and nerve root surgery (p=0.034; OR,1.54; 95%CI,1.02-3.43) associated with deep vein thrombosis (Table1).

Table 2 shows multiple logistic regression analysis, complex regional pain syndrome was a significant predictor of deep vein thrombosis in the final multiple logistic regression model (p<0.001; OR,3.46 95%CI,2.02-6.95). In addition, cerebrovascular disease (p<0.001; OR,2.13; 95%CI, 1.05-3.49) also had significant association in this multiple logistic regression.

Table 1 Demographic data of study population

Characteristic	Total (N=480)	Deep vein thrombosis group (N=87)	No Deep vein thrombosis group (N=393)	P value	OR	95%CI
Male gender, N(%)	245(51.0)	44(50.6)	201(51.1)	0.845	0.95	0.62-1.65
Age (years, mean)	68.2	67.1	68.4	0.534	0.99	0.98-1.02
Diabetes mellitus, N(%)	267(55.6)	45(51.7)	222(56.5)	0.787	0.98	0.97-1.04
Malignancy, N(%)	85(17.7)	19(21.8)	66(16.8)	0.042	1.52	1.04-1.74
Cerebrovascular disease, N(%)	111(23.1)	32(36.8)	79(20.1)	<0.001	2.17	1.49-4.01
Spinal cord disease, N(%)	117(24.3)	13(14.9)	104(26.5)	0.021	0.79	0.61-0.96
Nerve root disease, N(%)	167(34.8)	23(26.4)	144(36.6)	0.556	0.96	0.92-1.02
Complex regional pain syndrome, (%)	47(9.7)	26(31.0)	21(5.3)	<0.001	4.25	1.99-6.43
Paralysis or paresis of lower limb, (%)	480(100.0)	87(100.0)	393(100.0)	-	-	-
Brain surgery, (%)	116(24.2)	23(26.4)	93(23.7)	0.834	1.12	0.62-1.36
Spinal cord surgery, (%)	31(6.5)	6(6.9)	25(6.3)	0.659	1.00	0.99-1.01
Nerve root surgery, (%)	70(14.6)	18(20.7)	52(13.2)	0.034	1.54	1.02-3.43
D-dimer, (microgram/liter, mean)	892.5	875.0	934.5	0.748	0.98	0.96-1.02

Table 2 Associations between the risk factors and deep vein thrombosis by multiple logistic regression analysis

Covariate	Coeff(b)	SE(b)	p value	OR	95%CI
Malignancy	0.027	0.024	0.255	1.03	0.98-1.08
Cerebrovascular disease	2.255	0.416	<0.001	2.13	1.05-3.49
Spinal cord disease	-0.027	0.038	0.475	0.87	0.75-1.05
Complex regional pain syndrome	1.500	0.407	<0.001	3.46	2.02-6.95
Nerve root surgery	0.92	0.385	0.811	1.10	0.52-2.33

Discussion

The results of our study suggested that complex regional pain syndrome (p<0.001; OR,3.46; 95%CI,2.02-6.95) and cerebrovascular disease (p<0.001; OR,2.13; 95%CI,1.05-3.49) were a significant predictor of deep vein thrombosis in the final multivariate logistic regression model. Stroke patients had a deep vein thrombosis incidence up to 80% and pulmonary embolism incidence up to 16%.[14] In previous study[15], complex regional pain syndrome coexistence with deep vein thrombosis could occurred in hemorrhagic stroke patients. In our study, cerebrovascular disease such as intracerebral hemorrhage or subarachnoid hemorrhage had significant higher in deep vein thrombosis group by univariate analysis and multiple logistic regression model, cerebrovascular disease might be predictor of deep vein thrombosis due to severe immobilized mechanism and a risk factor for complex regional pain syndrome due to location of disease that affecting central pain such as thalamus in thalamic hemorrhage patient who had uncontrol hypertension.

In previous study, malignancy is strong risk factor of deep vein thrombosis. A recent meta-

analysis[16] found that pancreatic cancer displayed the highest rate of venous thromboembolism, while other studies suggest that the highest incidence rates occur in mucin-producing adenocarcinomas of the pancreas, lung, and gastrointestinal tract.[17] In our study, malignancy was not associated with deep vein thrombosis in final multiple logistic regression model. This finding might be because our study was an observational study, thus, attending physician tended to select patients with early stage of malignancy for treatment by surgical treatment alone and all of these patients had brain tumor and no any patients with pancreatic cancer or mucin-producing adenocarcinomas tumor included in our study.

Patients with nerve root disease mostly had leg paralyzed that limited walking activity. In addition, nerve root surgery can cause complex regional pain syndrome due to traumatic mechanism. Nociceptive sensitization occurs early on, driven by the release of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-a) and prostaglandin E2.[18] This sensitization leads to a decrease in the depolarization threshold locally, likely contributing to hyperalgesia in these patients.[19] In our study, nerve root surgery associated with deep vein thrombosis but not statistically significance in final multiple logistic regression model that might be because of low proportion of nerve root surgery in our study.

D-dimer is detectable in patients with deep venous thrombosis, as it is a marker of endogenous fibrinolysis.[20] Clinicians must be aware that D-dimer is increased in many conditions. Physiologic causes of D-dimer elevation include pregnancy and puerperium, increasing age (>65 years), African American heritage, cigarette smoking, recent trauma, and the postoperative period.[21] In our study, D-dimer level was not associated with deep vein thrombosis, because in our study mostly patients who identified D-dimer level had leg edema after postoperative period, mostly patients in our study had old age and high proportion of cerebrovascular disease.

Deep vein thrombosis is a significant healthcare problem in general populations, especially in the paretic or paralysis patients. For the past 150 years, thoughts on the of venous thromboembolism centered on Virchow's triad of stasis, changes in the vessel wall, and thrombogenic changes in the blood. However, in the early 1970s, through the pioneering theories of Gwendylen Stewart, a relationship between thrombosis and inflammation was suggested. Stasis by itself, although an important factor, is usually not enough to produce thrombosis and should be considered a permissive factor in thrombogenesis for the other events that are required for thrombosis to occur.[22] Inflammation and thrombosis are interrelated. For example, inflammation increases tissue factor, platelet reactivity, fibrinogen, and leads to exposure of increased levels of phosphatidylserine, while decreasing thrombomodulin and inhibiting fibrinolysis (by increasing PAI-1).[23] Microparticles (MPs) are involved in the thrombotic process and the amplification of thrombosis. MPs are small (less than 1 micrometer, about the size of a bacterium), phospho-lipid vesicles shed from platelets, leukocytes, and endothelial cells in a calcium dependent fashion.[24-26] MPs are a normal constituent of blood and can be isolated from plasma by ultracentrifugation. MPs lack DNA and recent evidence suggests they may carry RNA[27], and they are protein rich. Subpopulations of MPs rich in TF and phosphatidylserine have been identified.[28,29]

Several circulating markers of inflammation once thought to be soluble are actually carried by MPs.[30] MP contribute to inflammation via their influence on cell-cell interactions and cytokine release, and MP also function in mediating vascular tone. In several disease states characterized by inflammation and vascular dysfunction, MP subpopulations are elevated, correlate with clinical events, and may have important roles in pathogenesis.[31]

Complex regional pain syndrome (CRPS) is a chronic neurologic condition resulting from a multiple insult, with a prevalence of approximately 5.4-26.2 per 100 000 person years.[32] It can be further divided into two subtypes, based on the absence (CRPS I, previously known as reflex sympathetic dystrophy) or presence (CRPS II, previously known as causalgia) of a major nerve injury. This condition is enigmatic in nature. It has been historically difficult to diagnose and the pathophysiologic mechanism behind its development has not been clearly defined. CRPS is thought to be an elaborate combination of different factors that begin to take place at the time of initial injury, including nervous system sensitization, autonomic dysfunction, and inflammatory changes.[33] In our study, all of patients had neurological disorders. This study showed that CRPS is a neurological condition and may be risk factor for deep vein thrombosis due to interrelated inflammation- thrombosis theory.

Conclusion

This present study suggests that the complex regional pain syndrome and cerebrovascular disease were predictors of deep vein thrombosis in neurological disorder patients. More patients need in further study to prove hypothesis that interrelated inflammation-thrombosis theory can cause deep vein thrombosis.

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