Singapore Med J 2009; 50(10) : 971

Deep vein thrombosis based on D-dimer screening in ischaemic stroke patients undergoing rehabilitation

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ABSTRACT

Introduction: Although lower extremity deep vein thrombosis (DVT) is a common complication after an acute stroke, there is little local data documenting this condition in stroke patients undergoing rehabilitation. The purpose of this study was to determine the frequency and risk factors of DVT in ischaemic stroke patients admitted to a rehabilitation unit.

Methods: This was a prospective observational single-centre study of ischaemic stroke patients with lower limb paresis admitted to a rehabilitation centre. The screening protocol consisted of quantitative D-dimer assay (DDA) within 24–48 hours of rehabilitation admission followed by duplex Doppler ultrasonography (DUS) of the paretic lower extremity if the DDA level was elevated (equal or greater than 0.34 µ/ml).

Results: 212 patients (167 Chinese, 27 Malays, 17 Indians and one Eurasian) were screened at a mean of 23.2 days post-stroke. 121 (57.1 percent) patients had an elevated DDA, and all underwent ultrasonography. The incidence of lower limb DVT was 5.2 percent (11), consisting of four proximal and seven distal. DVT was significantly related to total anterior circulation infarct (odds ratio 3.69, 95 percent confidence interval 1.04–3.05, p-value is 0.043), but not to age, gender, race, severity of lower limb weakness, and ambulatory and functional status. No patients had clinical pulmonary embolism during rehabilitation.

Conclusion: Locally, asymptomatic lower limb DVT based on a screening protocol of DDA and selective DUS, is uncommon in ischaemic stroke patients admitted to rehabilitation. Future research efforts could include a detailed evaluation of DDA's role as a screening tool for DVT in the stroke population, by comparing it to an established gold standard like venography.

Keywords: D-dimer, deep vein thrombosis, stroke, rehabilitation

Singapore Med J 2009;50(10):971-975

INTRODUCTION

Studies have shown that the incidence of lower extremity deep vein thrombosis (DVT) is common following an acute stroke, with incidence rates as high as 40%–50%.[1-3] In patients undergoing rehabilitation, the frequency of DVT has been reported to be as high as 33%.[4] Early detection of DVT is important because of the risk of pulmonary embolism and its potentially fatal consequences. However, it is well known that clinical features of DVT and pulmonary embolism are notoriously nonspecific. This diagnostic conundrum is even more challenging in stroke patients who may under-report symptoms due to aphasia, neglect, cognitive impairment or altered conscious states. Given the above, there is a case to be made for the routine screening of DVT in patients undergoing rehabilitation.

Of the various radiological tools for diagnosing DVT, Doppler ultrasonography (DUS) is probably the commonest tool used as it is convenient and noninvasive. However, as a screening tool for asymptomatic DVT, it is costly and time-consuming. More recently, some investigators have used D-dimer assay (DDA) as a screening test for asymptomatic DVT.[5-8] D-dimers are derived from cross-linked fibrin breakdown products generated from the degradation of the fibrin matrix of fresh venous thromboemboli, and are thus elevated in patients with DVT. When used in combination with DUS, sensitivity and negative predictive values of 100% have been reported in stroke patients undergoing rehabilitation.[5] Hence, DDA may be a reliable and useful screening test for DVT and allows for the identification of a subgroup of patients to undergo targeted limb imaging.

The primary objective of this study was to determine the frequency of DVT based on a screening protocol of DDA and selective DUS in ischaemic stroke patient admitted to our rehabilitation centre. The secondary objective was to study the clinical characteristics and factors associated with DVT.

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METHODS

This was a prospective, observational study of consecutive ischaemic stroke patients admitted to our rehabilitation centre between May 2005 and December 2006. The diagnosis of stroke was confirmed in all the cases by computed tomography and/or magnetic resonance imaging of the brain. Patients with a recurrent stroke were also studied. Excluded were patients with no lower extremity motor deficit or were already diagnosed with DVT. All the patients received thigh-length graduated pressure compressive stockings for both lower limbs on admission to rehabilitation, to be worn until discharge as a routine non-pharmacological DVT prevention. Subcutaneous low-molecular-weight heparin (LMWH) prophylaxis is not part of the standard practice for patients with severe limb paresis in our centre. However, LMWH was continued if it was commenced at the acute stroke unit, and discontinued when patients were ambulatory for 20 m with or without aid. The study was conducted with the approval of the ethics committee of the hospital's institutional review board.

The DVT screening protocol was implemented in our centre in May 2005. This consisted of DDA and selective DUS. Blood was taken for DDA within 24 hours of the patient's admission to the rehabilitation unit. DDA was measured using a commercial assay known as the LIATEST D-Dimer assay (Diagnostica Stago, Asnières-sur-Seine, France), which is an immunoturbidimetric quantitative assay based on latex microparticle agglutination. The diagnostic accuracy of this assay has been validated by several studies.[9,10] DUS of the hemiplegic lower extremity was performed if the DDA was elevated. An elevated DDA was defined as > 0.34 μ/ml. This cut-off reference point was based on DDAs obtained from 200 healthy hospital workers.

All DUS studies were performed in a single radiology department by the same radiographer with specific experience, and reported by trained radiologists using a Toshiba Xario venous Doppler ultrasound machine version 2002 (Toshiba America Medical Systems, Tustin, CA, USA), during the study period. DUS combines conventional grey-scale ultrasonography with colour and spectral Doppler analysis of vessels. A standard protocol using accepted compression techniques and Doppler criteria for DVT diagnosis, was used. DUS was done within a week of the DDA result. In patients with a bilateral lower limb weakness, both lower limbs would be screened. The presence of DVT was determined by a positive DUS result of either proximal or distal DVT. DVT was classified into proximal (iliac, common superficial and deep femoral and popliteal vein involvement) or distal (posterior tibial, peroneal, gastrocnemius, soleal and perforator vein involvement).

Data of interest included the patient's demographics, selected medical comorbidities (congestive cardiac failure, atrial fibrillation and history of cancer), stroke characteristics (nature and site of stroke), use of subcutaneous heparin for DVT prophylaxis, neurosurgical operations and use of antiplatelet or anticoagulant treatment for secondary prevention of stroke in patients with an ischaemic stroke. The Oxfordshire Community Stroke Project classification[11] was used to classify the stroke location.

Rehabilitation data studied included: (1) Severity of lower limb weakness using the motricity index. This was calculated by measuring the best motor power of the hip, knee and ankle using the Medical Research Council grading, and summating them. The score ranged from 0 to 15, with 15 indicating no motor weakness. (2) Functional status on admission using the Functional Independence Measure (FIM).[12] The total FIM score is a global indicator of functional impairment and burden of care. It consists of 18 individual categories, and each category is scored from 1 to 7, where the higher the score, the more independent the patient. Scores of 1–2 indicate complete dependence, 3–5 modified dependence and 6–7, independence. The total FIM score ranges from 18 to 126. (3) Ambulatory status of the patient. This was evaluated using the FIM-walk category of the FIM and classified as follows: non-ambulatory (FIM-walk scores of 1–2), ambulatory with assistance (FIM-walk score of 3–5) and ambulating independently (FIM-walk score of 6–7). These measures were evaluated within 72 hours of rehabilitation admission.

Statistical analysis was carried out using the Statistical Package for Social Sciences version 14.0 (SPSS Inc, Chicago, IL, USA) and STATA 9.2 (StataCorp, College Station, Texas, USA). All statistical tests were carried out at a 5% level of significance. Our outcomes of interest were D-dimer levels (elevated or not) and the presence of DVT, both of which were dichotomous. The following covariates were studied: age, gender, ethnicity, site of stroke (total anterior circulation infarct vs. others), atrial fibrillation, congestive cardiac failure, stroke prevention treatment (antiplatelet/anticoagulants vs. none), neurosurgical operations, DVT prophylaxis with heparin, length of stay in acute facility, lower extremity motricity index (LEMI), ambulatory status (non-ambulatory and ambulatory with assistance based on the FIM-walk score), FIM-total and D-dimer levels. Continuous covariates that were not normally distributed, were categorised using standard quartiles. The logistic regression model

Table I. Clinical characteristics of the study cohort.

Clinical characteristic	No. (%) of patients* (n = 212)
Mean age and SD (years)	63.4 ± 12.7
Gender	
Male	127 (59.9)
Female	85 (40.1)
Race	
Chinese	167 (78.8)
Malay	27 (12.7)
Indian	17 (8.0)
Eurasian	1 (0.5)
Comorbidity	
Hypertension	177 (83.5)
Diabetes mellitus	97 (45.8)
Ischaemic heart disease	50 (23.6)
Previous stroke	46 (21.7)
Congestive cardiac failure	13 (6.1)
Atrial fibrillation	23 (10.8)
History of cancer	11 (5.2)
Site of infarct	
Total anterior circulation infarct	47 (22.2)
Partial anterior circulation infarct	41 (19.3)
Posterior circulation	46 (21.7)
Lacunar	78 (36.8)
Mean length of stay and SD (days)	
In acute facility	23.2 ± 40.1
In rehabilitation	29.9 ± 15.0
Lower extremity motricity index score	
Very severe weakness (0–3)	59 (27.8)
Moderately severe weakness (4–6)	22 (10.4)
Moderate weakness (7–9)	42 (19.8)
Mild weakness (10–14)	89 (42.0)
Mean FIM (total) score and SD	58.6 ± 23.6
FIM-walk score	
Non-ambulatory (1–2)	95 (44.8)
Ambulating with assistance (3–5)	117 (55.2)
D-dimer level	
Mean and SD	1.15 ± 2.2
< 0.34	91 (42.9)
≥ 0.34	121 (57.1)

* unless otherwise specified
SD: standard deviation

Table II. Univariate analysis of factors associated with an elevated D-dimer assay.

Variable	Odds ratio	95% confidence interval	p-value
Age*	1.02	1.00–1.05	0.015
Gender†	2.84	1.57–5.10	0.0001
FIM-total‡	0.97	0.96–0.99	< 0.001
Ambulatory status§	0.42	0.24–0.75	0.003
Site of infarct¶	2.06	1.02–4.13	0.041

* every year increase in age
† female vs. male
‡ every unit increase in FIM score
§ ambulatory with assistance vs. non-ambulatory
¶ total anterior circulation infarct vs. others

was used to perform both the univariate and multivariate analysis. Both the crude and adjusted odds ratios, and their associated 95% confidence intervals were presented as estimates of effect sizes.

RESULTS

A total of 214 patients with an ischaemic stroke underwent DVT screening during the study period. Of these, two patients were diagnosed with DVT in the referring neurological service and were excluded from the study. 212 patients underwent DVT screening, none of whom were symptomatic or had clinical signs on examination for DVT on admission, as assessed by the attending medical team. The clinical characteristics of the patients are shown in Table I. The study cohort was relatively young, with a mean age of 63.4 ± 12.7 years. Chinese patients formed the majority, followed by Malays and Indians. The racial distribution is similar to that of the general population. The mean admission LEMI and FIM-total scores were 7.4 ± 4.8 and 62.7 ± 22.4, respectively. Slightly less than half of the patients (44.8%) were non-ambulant on admission to rehabilitation (FIM-walk score of ≤ 2) and 55.2% needed varying degrees of assistance for walking (FIM-walk score of 3–5). No patient had a FIM-walk score of 6 or 7. Eight (3.8%) patients underwent neurosurgical procedures. Only seven patients were given subcutaneous heparin for DVT prophylaxis. Lacunar stroke was the commonest (36.8%), followed by total anterior circulation stroke (22.2%), posterior circulation stroke (21.7%) and partial anterior circulation stroke (19.3%). With regard to stroke prevention, antiplatelet therapy was given to 185 patients, anticoagulant therapy to 14, and none to 13 patients.

DDA was elevated in 121 (57.1%) patients. Univariate analysis showed that older patients, female gender, total anterior circulation infarct, non-ambulatory status and low admission FIM-total score were associated with an elevated DDA (Table II). On multivariate logistic regression, only FIM-total score (odds ratio [OR] 0.97, 95% confidence interval [CI] 0.96–0.99, $p < 0.001$) and female gender (OR 2.70, 95% CI 0.47–4.96, $p = 0.001$) were significant independent predictors of an elevated DDA.

DUS was performed in all 121 patients with an elevated D-dimer level. DVT was diagnosed in 11 (5.2%) patients, i.e. proximal DVT in four patients and distal DVT in seven patients. Three patients with proximal DVT were anticoagulated and one had inferior vena cava filter insertion because of contraindication to anticoagulation. In patients with distal DVT, the decision to repeat DUS and treat DVT was decided by the primary physician in charge and depended on factors like the severity of lower limb paresis, the patient's mobility and the development of symptoms. Only one patient with distal DVT was anticoagulated, and two underwent repeat DUS, which

revealed resolution of the DVT. In the 91 patients with normal DDA, none developed symptomatic or clinically-significant DVT during the inpatient rehabilitation stay. There was also no documented case of suspected pulmonary embolism in all 212 patients. Univariate analysis of clinical variables showed that only total anterior circulation infarct was correlated to DVT (OR 3.69, 95% CI 1.04–3.05, p = 0.043). Although the type of stroke prevention treatment is not related to DVT, it is worth noting that none of the patients who were anticoagulated or given subcutaneous heparin for DVT prophylaxis had DVT.

DISCUSSION

This study showed that DVT is relatively uncommon in a cohort of ischaemic stroke patients undergoing rehabilitation. This finding is in marked contrast to that reported by De Silva et al. They screened 105 consecutive ischaemic stroke patients admitted to a local neurological service for DVT with DUS, and reported DVT rates of 30% and 45%, respectively, at days 7–10 and at days 25–30 post-stroke. In the 42 patients with DVT at days 25–30 post-stroke, 15 did not have DVT on the initial DUS.[13]

This observation can be explained by differences in screening protocol and patient selection. Firstly, in the study by De Silva et al,[13] DUS of both lower limbs was routinely performed in all patients, regardless of the side of hemiplegia. This was likely to result in a higher DVT pick-up rate, as DVT can also occur in the non-paretic lower limb. This was confirmed by the finding that 13% of DVT occurred in the non-paretic lower limb. Secondly, routine DUS was performed on all patients, as opposed to DUS based on an elevated DDA as in our study. Although the sensitivity of DDA for excluding DVT is high, it was possible that there were patients with DVT despite having a normal D-dimer level, leading to our underestimation of the actual incidence of DVT. Thirdly, compared to the unselected nature of patients in De Silva et al's study, the patients in our study were pre-selected based on the potential to benefit from rehabilitation and the ability to tolerate about three hours of rehabilitation a day. Hence, it is not surprising that our patients as a group were considerably younger (median age of 62 vs. 72 years) and were likely to be less neurologically and functionally impaired.

While factors like older age, severe paresis, atrial fibrillation, and poor functional and ambulatory status[1-3] have been reported to be associated with DVT in stroke patients, we were unable to identify any of the above risk factors associated with DVT in our study. The only clinical variable related to DVT was the presence of a total anterior circulation infarct. It is likely that patients with total anterior circulation stroke have a more severe stroke, and stroke severity is a risk factor for DVT. When interpreting these findings, it is necessary to bear in mind the small number of patients with DVT in this study, as this can either mask meaningful or produce spurious associations.

This study does have several methodological limitations. Firstly, the cut-off range for DDA used in our institution at the time of the study was obtained from 200 healthy hospital workers, and not substantiated by studies of a comparative hospitalised population. Secondly, there was a failure to scan the non-paretic limb and to perform routine follow-up imaging. These could have led to the low DVT rate observed. One must also recognise that although DUS is reliable in detecting symptomatic proximal DVT, a meta-analysis of high-risk postoperative orthopaedic patients in 11 studies indicated that the sensitivity for the diagnosis of asymptomatic proximal DVT was only 62%, and that for asymptomatic below-knee DVT, 48%.[14] The sensitivity of DUS in diagnosing asymptomatic DVT in stroke patients has not been previously evaluated. A possible alternative noninvasive imaging technique is that of magnetic resonance direct thrombus imaging. This directly visualises methaemoglobin within venous thrombi and has excellent sensitivity and specificity.[15] However, it is costly and requires a long examination time. Finally, as patients in this study were preselected based on their potential to benefit from rehabilitation, one must be cautious about generalising the results of this study to other stroke groups.

In this study of a select group of ischaemic stroke patients admitted to a rehabilitation centre, the frequency of asymptomatic DVT, based on a screening protocol of DDA and selective DUS, was relatively low at 5.2%. Future research efforts could include detailed evaluation of DDA's role as a screening tool for DVT in the stroke population by comparing it to an established gold standard like venography, and possibly validating the sensitivity of DUS in diagnosing asymptomatic DVT in stroke patients with a comparison test like magnetic resonance direct thrombus imaging.

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