Original Article

Early Deep Vein Thrombosis: Incidence in Asian Stroke Patients

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Abstract

Introduction: Deep venous thrombosis (DVT) is thought to be less common in Asians than in the Caucasian population. The incidence of asymptomatic DVT in high-risk groups in the Asian population has not been well studied. While DVT incidence among Caucasian stroke patients has been extensively studied and the need for prophylaxis established, the lack of data in Asian patients leaves physicians with no firm basis for adopting prophylactic protocols in the local population. Our aim was to prospectively establish the incidence of early DVT in immobilised stroke patients in a heterogenous Asian population. **Materials and Methods:** We screened 44 patients with significant hemiplegia from acute stroke. Doppler ultrasound, the currently accepted method of investigation for DVT, was used to study patients on admission and at 1 week post-stroke. While there was no standard prophylactic regime in use, none of the patients received heparin and only 2 were given compression stockings. **Results:** The incidence of DVT at 1 week was 2.4%. Review at 1 month detected another patient with DVT, bringing the overall incidence at 1 month to 4.8%. This is lower than in Caucasian populations, but is similar to another local study on a different group of high-risk patients. **Conclusion:** The low incidence of early DVT in hospitalised stroke patients of Asian ethnicity does not justify routine screening for this population. Further research to validate this should ideally include a comparison test for DVT as ultrasound may have inherently lower sensitivity in an asymptomatic population.

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Introduction

Deep venous thrombosis (DVT) is part of the spectrum of venous thromboembolism (VTE), with thrombi in the limbs predisposing to pulmonary embolism (PE). Immobility is an important risk factor for VTE, and patients with reduced mobility from a wide variety of causes are particularly vulnerable.[1] In stroke patients, PE is the most common cause of death between the second and fourth weeks.[2] DVT is often asymptomatic;[3] PE may occur without clinical signs.[4] It is therefore important to detect and treat occult DVT.

Although the incidence of DVT in stroke patients has been widely studied among Caucasians, its incidence in the Asian population is less well established. It has been thought that the incidence of DVT in Asians, particularly the Chinese, is lower compared to that of Caucasian populations. However, it is now believed that this is either increasing or that the condition had been previously underdiagnosed.[5] To date, there has been a paucity of published data on the incidence of DVT among at-risk groups of Asian patients.

Various imaging studies such as venography, impedance plethysmography and radioactive iodine (I^{125}) fibrinogen uptake tests were previously used to detect DVT. DVT can now be easily and non-invasively studied using Doppler ultrasound, the accuracy of which has been established.[6] We undertook a prospective Doppler ultrasound study to investigate the incidence of leg DVT in an Asian population

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of patients immobilised by stroke.

Materials And Methods

Patients with stroke [based on World Health Organization (WHO) criteria and CT brain performed within 24 hours of admission] were recruited from our 1100-bed general hospital in central Singapore. Subjects were included in the study if they were evaluable within 48 hours after an acute stroke and had lower limb weakness [defined as proximal power in at least one lower limb being less than Grade 3 on the Medical Research Council (MRC) rating scale]. Exclusion criteria included immobility before stroke onset and existing clinical suspicion of DVT. Initial clinical assessment of limb power and predisposing factors that might lead to a procoagulant state were recorded. Informed consent was obtained from the patient or a close relative in situations when the patient was not able to give written consent. Approval was obtained from the hospital's Research and Ethics Committee.

Doppler ultrasound was performed by a radiologist (SST or CCTL), using an Acuson Sequoia ultrasound system (Siemens Medical Solutions USA, Inc.) with a 5 to 8 mHz linear transducer. Doppler ultrasound combines conventional grey-scale ultrasound with colour and spectral Doppler analysis of vessels. A standard protocol using accepted compression techniques and Doppler criteria for DVT diagnosis was used.[7,8] The common femoral veins to the deep calf veins of both limbs were studied. Its accuracy within our facility has been established in a comparison study with venography.[9]

All patients underwent an initial Doppler ultrasound study of both legs within 48 hours of stroke to exclude any pre-existing venous disease. A second follow-up study was performed 1 week after admission. This timing was chosen as it has been shown that the majority of DVT following stroke occur[10] between 2 and 7 days after onset. At this time, clinical review was also performed for any change in limb power and clinical features of DVT or PE. Details of thromboprophylaxis (anticoagulants or compression stockings) were noted.

At 1 month post-stroke, a casenote review was carried out to detect the occurrence of major thrombotic events among study patients. Data were entered into an Excel spreadsheet and analysed using SPSS for Windows v11.0.

Results

We had planned to enrol 100 stroke patients, but due to logistic problems arising from the relocation of neurology patients to a new hospital site, only 44 patients could be recruited before the study was terminated. There were 22 male and 22 female patients with a mean age of 66.9 years [standard deviation (SD), 12.62; range, 35.0 to 92.0]. The racial distribution was 37 Chinese, 5 Malay, and 2 Indian patients. Based on intracranial CT scan, 23 had cerebral infarction, and 14 had cerebral haemorrhage, while 7 with normal studies were deemed to have had an ischaemic stroke. Within the first week, 2 patients died of severe subarachnoid haemorrhage and extensive cerebral infarction. The remaining patients with non-haemorrhagic stroke were treated with aspirin, dipyridamole or ticlopidine; none was given heparin. Only 2 patients were given compression stockings in the first week after stroke. None had evidence of acute or chronic DVT on initial Doppler ultrasound. Doppler ultrasound 1 week after stroke detected deep vein thrombosis (DVT) in 1 of 42 patients [2.4%; 95% confidence interval (CI), 0.4% to 11.8%]. On casenote review at 1 month, a second patient was found to have developed DVT (4.8%; 95% CI, 1.3% to 15.8%). Our 2 positive cases are described below.

Case 1

A 35-year-old Indian man was admitted to hospital with left middle cerebral territory infarction. He had no significant past medical history or known factors predisposing to a procoagulant state. On admission, he had MRC grade 1/5 power on the right-sided limbs, which subsequently deteriorated to grade 0 at 1 week. Doppler ultrasound on admission was negative for DVT (Fig. 1). He was treated with aspirin 300 mg OM. One week after admission, Doppler ultrasound revealed an echogenic thrombus distending the right popliteal vein and extending up to the mid superficial femoral vein (Figs. 2 and 3). There were no clinical signs or symptoms of DVT or PE. He was treated with intravenous heparin and oral warfarin. A follow-up study 2 weeks later showed almost complete resolution of the thrombus.

Case 2

This 55-year-old Indian lady, who had a history of diabetes mellitus, suffered a left frontal infarct and MRC grade 0/5 power on the right side. Both ultrasound studies on admission and at 1 week were negative. Whilst on a regime of aspirin and dipyridamole, she developed swelling and tenderness in the contralateral leg 3 weeks after admission. Doppler ultrasound confirmed left leg DVT up to the external iliac vein. She had no signs or symptoms of pulmonary embolism; arterial blood gas analysis was normal. She was also treated with heparin and discharged with warfarin. Repeat ultrasound 6 months later showed features of chronic DVT with recanalisation.

Discussion

Incidence of DVT in Stroke

Our study found the frequency of DVT among acute stroke patients of Asian origin to be 2.4% at 1 week and
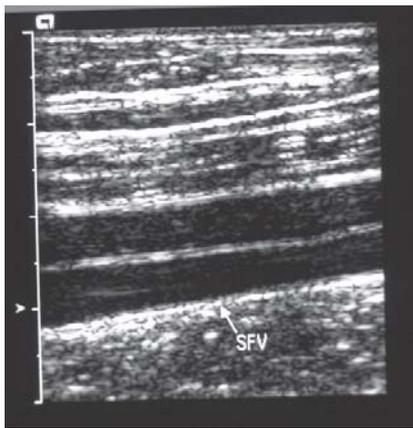
Fig. 1. Normal ultrasound study of Case 1 on admission. Longitudinal view. Arrow indicates the superficial femoral vein (SFV).

Fig. 2. Ultrasound study of Case 1, 1 week after stroke. Longitudinal view. The upper edge of the thrombus (arrow) can be seen in the superficial femoral vein in the mid thigh.
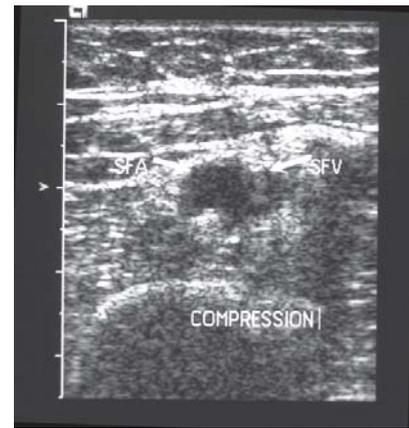
Fig. 3. Ultrasound study of Case 1, 1 week after stroke. Transverse view. The superficial femoral vein (SFV) cannot be compressed due to the presence of thrombus within. SFA: superficial femoral artery.

4.8% at 1 month, among patients with significant lower limb weakness. Both occurred in patients with ischaemic stroke. This is considerably lower than the published rates of DVT incidence in the Caucasian population (Table 1). In early studies using I^{125}, Warlow et al[11,12] reported DVT incidences of 60% and 53% in stroke patients. Studies using other techniques found 35%[13] (impedance plethysmography) and 34% to 36%[14] (venography) incidence. A review[10] combining the data of 5 studies with a total of 225 patients has reinforced this, with DVT incidence of about 50% within the first 2 weeks of stroke. Studies on patient groups selected by stroke aetiology showed similar incidence.[10] Minor trauma to the veins due to reduced sensation and muscle weakness, as well as loss of calf muscle pump function, probably contribute to increased susceptibility to DVT.[19]

VTE in Asian and Caucasian populations

The incidence of venous thromboembolism in the Asian population has been previously thought to be low compared to Caucasians. An epidemiological study using public healthcare data from an ethnic Chinese database of 6.7 million[20] showed overall annual incidences of 17.1 and 3.9 per 100,000 population for DVT and PE respectively. In comparison, the University of Massachusetts Worcester study[21] involving 16 hospitals found DVT and PE in 48 and 23 per 100,000 population respectively, and a single-city community study in Malmö, Sweden, found an even higher DVT rate of 159 per 100,000 population.[1]

However, some studies appear to show a rising trend in the Asian population.[5] Earlier autopsy studies in the Hong Kong Chinese population showed pulmonary thrombo-

Table 1. Deep Vein Thrombosis (DVT) Incidence in Stroke Patients

Study author/year/reference	No. of patients	Patient type	DVT test	DVT incidence (%)
Warlow et al/1972/[11]	30	Caucasian	I^{125}	60
Warlow et al/1976/[12]	76	Caucasian	I^{125}	53
Izzo and Aquino/1986/[13]	20	Caucasian	Impedance plethysmography	35
Sandset et al/1990/[14]	92	Caucasian, prophylaxis trial	Venography	36 (on heparin) 34 (on placebo)
Brandstater et al/1992/[10] (5 studies combined)	225	Caucasian	I^{125}	50
Pambianco et al/1995/[15]	360	Caucasian, prophylaxis trial	Doppler ultrasound	5.5
Muir et al/2000/[16]	97	Caucasian, prophylaxis trial	Doppler ultrasound	10 (given stockings) 21 (no stockings)
Tso/1980/[17]	35	Chinese	I^{125}	17
Sun et al/2004/[18]	488	Chinese	Doppler ultrasound	21.7
Present study	42	Chinese, Malay, Indian	Doppler ultrasound	4.8

embolism prevalence of 0.75[22] and 2.1%;[23] a Singapore autopsy study reported prevalence of 1.05%.[24] These are lower than those in similar studies done in the United States (3.8% to 9.3%).[25] However, a more recent study from Hong Kong showed an increased prevalence of 4.7%,[26] which is comparable with that of Caucasian patients. In Singapore, a comparison of 2 studies on hospitalised patients also shows an apparent increase in DVT incidence over time. A retrospective study in 1997[27] reported a DVT incidence of 15.8 per 10,000 admissions in a large general hospital, compared to 7.9 per 10,000 reported in an earlier study in 1992.[28]

There have been very few studies on the incidence of DVT in Asian patients with stroke. In 1980, Tso[17] reported asymptomatic DVT in 6 out of 35 Chinese patients studied (17%). I[125] was used in this study and patients were studied up to 1 week post-ictus; 5 patients suffered DVT in the paralysed leg, and 1 in the non-paralysed leg. More recently, a Doppler ultrasound screening study found a 21.7% incidence in 488 cases[18] of hospitalised stroke patients in a Chinese population. The first ultrasound was performed 7 to 10 days post-ictus, and a second study was performed on patients suspected to have DVT a week after that. The authors also found poor correlation with clinical signs and symptoms, and a higher incidence in older patients and those with a greater degree of paralysis, which were similar to Western reports.[19]

Although both studies in Chinese stroke patients reported a lower incidence compared to Caucasian studies, our present study, which was carried out among a mixed Asian population, shows an even lower incidence of DVT. A DVT screening study of neurosurgical patients[29] has also been performed in Singapore. This study, which was similar in design to ours, examined 106 patients with brain tumours with a preoperative ultrasound scan of both legs, and a postoperative scan between day 5 and day 7. The incidence of DVT was 4.7%, which is comparable to the present study. Of the 5 patients who developed DVT, 4 of them developed it in the previously hemiparetic limb. Other multiethnic studies performed in Singapore found a very low symptomatic DVT incidence of 0.7%[30] among stroke patients, and 0.9%[31] among patients going for elective surgery, despite the underutilisation of VTE prophylaxis.

Prophylaxis and Screening

It is known that clinical findings are unreliable in DVT,[3] and stroke patients may have additional difficulty highlighting symptoms and signs if there is impaired mental status or aphasia. Only 38% of patients with DVT confirmed by I[125] uptake tests had positive clinical features.[10] Hence, there has been a long search for a safe means of prophylaxis and an accurate, non-invasive means of testing. There is no

standard approach to this in local hospitals, clinicians often combining individual preference and clinical acumen in determining whether to give prophylaxis or to order a DVT test. Consistent with current acceptance of the efficacy of heparin and compression stockings,[32] local clinical practice includes the prophylactic use of above-knee DVT stockings and, less frequently, subcutaneous unfractionated or low-molecular-weight heparin injections, particularly among patients with a lower limb too weak to overcome gravity (MRC grade less than 3). A recent study demonstrated that low-molecular-weight heparin (Lovenox) was more effective compared to unfractionated heparin, and this method of treatment may be more frequently used in the future.[33] Pneumatic calf pumps are hardly used. The problems with these measures include patient discomfort with stockings and pumps, particularly in our warm weather, and bleeding risk and pain with the heparins.

Screening Tests for DVT[34]

While the Western literature advocates a more anticipatory approach to VTE in stroke,[19,35] suggesting screening studies using Doppler ultrasound[15] or d-dimers,[36] the lack of Asian data on DVT incidence in stroke made it uncertain if any form of screening was necessary or could be justified locally.

I[125] uptake tests were extensively used for DVT screening in the past as it could be easily performed by the bedside using intravenously injected labelled fibrinogen and portable equipment. However, while it was very sensitive and specific for calf thrombi, it was hampered by limited sensitivity in the proximal veins due to tracer in larger veins and the bladder. Radiation exposure precluded its use as a serial monitoring test, and the risk of transmitting blood-borne diseases made it an unfavourable test; I[125] uptake is no longer commercially available in the United States. Impedance plethysmography is a simple non-invasive test which measures mechanical obstruction to blood flow in veins. It has high sensitivity for proximal vein thrombosis but is insensitive for calf thrombi and small thrombi, and lacks specificity. Venography was the gold standard for the investigation of symptomatic DVT, prior to the development of ultrasound. However, it involves radiation exposure, carries intravenous contrast medium risks, and requires transfer to the radiology department, making it poorly suited as a screening method in severely ill patients.

Doppler ultrasound has now replaced venography as the investigation of choice for DVT in symptomatic patients; it has an overall sensitivity of 95% to 98%[6,37] and a calf vein sensitivity of 95%.[38] While its portability and non-invasive nature make it an easy test to use on stroke patients, there is some concern that it may have an inherently lower sensitivity in an asymptomatic population. Studies utilising

Doppler ultrasound for DVT screening trials on stroke patients have shown incidences of 5%[15] to 21%,[16] which are lower than screening studies previously performed using other imaging methods. Sensitivity of only 50% has been cited in ultrasound screening of neurosurgical patients.[39] In a meta-analysis of 17 ultrasound studies on orthopaedic surgery patients,[40] sensitivity of 62% was reported in the level 1 (minimal bias) studies. It was postulated that the lower sensitivity could be due to the thrombi being usually small and non-occlusive.

Alternative tests for VTE investigation in the future include magnetic resonance (MR) imaging and d-dimer assays. MR venography[41] is non-invasive and can image both lower limbs, pelvic veins and the inferior vena cava in one study. It compared favourably with venography in a small study of symptomatic DVT.[42] MR venography may also be combined with MR direct thrombus imaging, which directly visualises methaemoglobin within venous thrombi with excellent sensitivity and specificity.[43] The disadvantages of MR imaging at present, however, include its high cost and long examination time. D-dimer assays are non-imaging-based tests; they are based on the fibrin breakdown product generated from fresh venous thromboemboli. ELISA assays of d-dimers have shown a high sensitivity of 97% in symptomatic DVT,[44] but a low specificity of 35% to 45% (threshold 500 ng/mL). In a study on 105 rehabilitating stroke patients, 14 of whom had ultrasound-detected DVT, d-dimer assays showed 100% sensitivity and 66% specificity at a threshold of 1092 ng/mL.[36] In another study on 102 stroke patients, median d-dimer levels were significantly higher in those patients who developed DVT diagnosed by MR direct thrombus imaging.[45] However, there is currently a lack of uniformity between the results obtained from different commercial assays, and d-dimer elevation in the acute phase of ischaemic stroke may also contribute to spurious results.[19]

Limitations

Our study was limited by a small sample size, as we could not achieve our target of 100 patients. There was also a lack of uniformity of thromboprophylaxis given to the patients, as there was no standard protocol at our institution at that time. However, none of our patients received heparin, and only 2 had stockings for a short period. Our selection criterion of grade 3 limb power or below excluded patients with lesser degrees of paresis, and any asymptomatic DVT occurrences in this group would not have been represented. Furthermore, the incidence of VTE at 1 month post-stroke depended on symptomatic presentation, and clinically silent cases might have been missed. Future studies should be designed taking this into consideration, with continued surveillance into the later, stroke rehabilitation phase.

Doppler ultrasound may also under-detect DVT in asymptomatic patients. Further trials should ideally include a comparison test to validate the efficacy of any screening method.

Conclusion

In this small study of a mixed Asian population with stroke, we found a low incidence of DVT, which was similar to another local study on a different at-risk population. While our study population is small, with the possibility of reduced sensitivity of Doppler ultrasound in an asymptomatic population, our findings do not support the institution of early DVT screening with Doppler ultrasound for stroke patients in Singapore. Nevertheless, further studies are needed in this group, particularly in the rehabilitative phase.

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