ORIGINAL ARTICLE

Deep Venous Thrombosis in Stroke Patients during Rehabilitation Phase

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Abstract. Purpose: The purpose of this study was to examine the incidence, factors, and effects of antiplatelet and anticoagulant agents on sub-acute and chronic ischemic stroke patients during the rehabilitation phase for rates of deep venous thrombosis (DVT) from the perspective for rehabilitation medicine.

Methods: In this study of 272 patients undergoing rehabilitation for completed cerebral infarction, multiple circumference measurements of calf and thigh along with presence or absence of symptoms (congestion, swelling, skin redness, warmth, pain, pigmentation, fever and/or Homan sign or Luck's sign) documented in the physical examination were recorded in all patients. Patients with these symptoms suggestive of DVT were included for D-dimer assay and venous duplex ultrasonography to confirm presence of DVT.

Results: DVT was documented in 24 patients (8.8%), most of whom displayed distal DVT on the hemiparetic side. A significant association was seen between occurrence of DVT and more severe lower limb paresis, manifesting as gait disturbance, severe calf muscle spasticity, use of ankle-foot orthosis (AFO). A significant increase in development of DVT was associated with severe spasticity in hemiparetic calf muscles (odds ratio (OR) 28.2; 95% confidence interval (CI), 6.9-113.5). Cilostazol seemed to be the only effective antiplatelet drug for preventing DVT in cerebral infarction patients.

Conclusion: Incidence of DVT in the rehabilitation phase following stroke was not low, which was predominant as distal DVT on the hemiparetic side. Lower limb paresis, gait disturbance, calf muscle spasticity and use of AFO contributed to occurrence of DVT. It is likely that micro-injuries in the venous endothelium due to spasticity and AFO might cause DVT. Cilostazol seems effective for protecting against venous endothelial damage following DVT. (Keio J Med 57 (4) : 196–204, December 2008)

Key words: stroke, hemiparesis, deep venous thrombosis, antiplatelet drug

Introduction

Deep venous thrombosis (DVT) is a common complication in patients with acute thromboembolic stroke.[1,2] Incidence of DVT during the first 2 weeks after stroke has been reported at between 27% and 75% among untreated control patients in several randomized prophylaxis trials.[3] The incidence and clinical impact of DVT during the chronic rehabilitation phase following stroke are, however, less well appreciated. DVT is difficult to diagnose in rehabilitation patients, as the clinical signs and symptoms of this condition are nonspecific. Most cases are identified by Doppler ultrasonography, plethysmography or contrast venography, all of which are expensive and relatively time-consuming techniques. Recent studies have suggested that the latex D-dimer assay can be used to exclude DVT and pulmonary embolism (PE) more quickly and in a less costly manner than other methods.[4] Few reports have examined DVT during the chronic stroke rehabilitation phase and some studies

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have demonstrated that the prevalence of DVT is also high in patients with stroke who develop swelling of the hemiparetic limb during rehabilitation.[5,6] In another study of 102 consecutive patients undergoing rehabilitation for completed stroke, incidence of DVT was 11% at a mean of 60 days after stroke onset (median, 49 days; range, 14-138 days), with a 2% incidence of fatal pulmonary embolism.[7] A recent study detected lower extremity DVT in 34% of patients, and 23% of patients displayed isolated calf vein thrombosis among patients admitted to inpatient rehabilitation programs.[8] Several previous studies have suggested that DVT is less frequent among Asians than among Caucasians.[9] De Silva *et al*.,[10] however, reported that DVT following ischemic stroke among Asians is common and associated with poor functional outcome. As for medical factors associated with DVT in the rehabilitation phase, a history of cardiac arrhythmia appears to be associated with lower risk of DVT, while myocardial infarction, congestive heart failure, hypertension, diabetes mellitus, chronic heart failure and anemia are not significantly associated with risk of DVT.[11] Understanding the incidence and characteristics of DVT complicating chronic ischemic stroke is important, since the benefit of anticoagulation for prophylaxis or treatment of venous thromboembolism must be weighed against the risk of possible secondary hemorrhagic conversion of cerebral infarction and major hemorrhage. Aspirin should be routinely used soon after cerebral infarction, but its role as an adjunctive method to prevent DVT is unclear.

The present report examined the incidence, factors and effects of antiplatelet and anticoagulant agents on subacute or chronic ischemic stroke during the rehabilitation phase for rates of DVT from the perspective of rehabilitation medicine.

Methods

Patient Population

A total of 296 stroke rehabilitation patients admitted consecutively to freestanding rehabilitation hospitals between September 2005 and August 2007 were eligible for this study. The study included patients ≥18 years old who had suffered a stroke, whose primary reason for rehabilitation was disability resulting from stroke, and who were rehabilitation inpatients or outpatients for ≥3 days. Stroke, defined as an acute event of cerebrovascular origin, causing focal or global dysfunction lasting >24 hours, was confirmed by both clinical and radiographic evaluation. All patients admitted to university hospitals or rehabilitation hospitals after completed stroke were followed from admission to discharge and at the outpatient clinic for >2 months. Subjects were medically stable and able to participate in an active rehabilitation program. Inclusion criteria included: 1) ischemic stroke (diagnosed by a consultant neurologist based on clinical presentation and computed tomography (CT) or magnetic resonance imaging of the brain performed within 48 hours of symptom onset); and 2) Stroke Impairment Assessment Set (SIAS)[12] <5; for the lower limb affected by stroke at time of screening study. Exclusionary criteria were: 1) hemorrhagic stroke; 2) >50 weeks post-stroke; 3) active cancer; and 4) past history of DVT or PE. Medical histories were obtained on all patients through a review of medical records from the referring hospital and verification against medical assessment at rehabilitation centers. Physicians assessed the date of screening examinations, severity of weakness and level of mobility for all stroke patients on day of admission to the rehabilitation centers. The reviewers also identified use of antiplatelet agents and anticoagulants that were prescribed on transfer to rehabilitation center. All patient data were collected in accordance with the Declaration of Helsinki of 1975, as revised in 1983, and study protocols were approved by the local institutional review board.

Patient histories were reviewed to ascertain results of clinical examinations and Doppler studies. Multiple circumference measurements of the calf and thigh as along with presence or absence of symptoms (congestion, swelling, skin redness, warmth, pain, pigmentation, fever and/or Homan sign or Luck's sign) documented in the chart on the day of physical examination were recorded in all patients. Asymmetries in calf and thigh measurements were documented as an important clinical sign of DVT in patients in whom asymmetry exceeded 2.5 cm,[13] as the difference in calf diameter is reportedly useful for ruling in DVT, while absence of calf swelling or difference in calf diameter is useful for ruling out DVT.[14] Patients with these symptoms suggestive of DVT occurring at any time during rehabilitation were considered for inclusion in the study for D-dimer assay. The D-dimer assay is a reliable method for ruling out DVT. In the rehabilitation setting, this assay can be used as a routine screening test or to assess cases of suspected DVT. Venous duplex ultrasonography was used as a criterion measure to confirm presence of DVT, as these procedures are recommended as the "first-line" diagnostic instrument in evaluation of DVT.[15,16,17] Doppler ultrasonography studies were performed using a Phillips Advanced Technology Laboratory 5000 device with a 7.5-MHz linear probe. B-mode two-dimensional imaging was used to visualize and identify where the common femoral superficial and popliteal veins divide into multiple calf veins (calf trifurcation) of the lower extremity. Light probe compression, milking method and color flow analysis were used to investigate DVT. The supporting criterion for DVT was continuous low flow with decreased or no augmentation (using calf squeeze) on Doppler spectral analysis, and partial or complete vessel wall

Table 1

	Mean age(y)	sex, n	stroke type, n(%) (T)	(L)	(E)	Median SIAS (hip)	(knee)	(ankle)	Median MAS	Median gait FIM
DVT (+) (n=24)	68.0	M16, F8	18(75)	2(8.3)	4(16.7)	3	3	1	2	4
DVT (-) (n=248)	69.2	M162, F86	188(75.8)	26(10.5)	34(13.7)	3	3	2	1	4

DVT: Deep venous thrombosis, T: atherothrombotic infarction, L: lacuna infarction, E: cardiogenic embolism, SIAS: Stroke Impairment Assessment Set, MAS: Modified Ashworth scale, FIM: Functional Independent Measure

compression failure.[18] Lack of vein compressibility was the sole diagnostic criterion for diagnosis of DVT.[19] Thrombi identified in the common, deep and superficial femoral veins, as well as those found in the popliteal vein, were classified as proximal DVTs. Calf DVTs included those involving the tibial, peroneal, soleal, gastrocnemius, and perforator veins. Thrombosis below the popliteal vein was categorized as distal DVT.

SIAS score[12] was assessed for the paretic lower limb by certified trial coordinators. If both lower limbs were paretic, SIAS score of the weaker limb was recorded. Foot and leg function were staged according to SIAS. Ultrasonography studies and SIAS scoring were performed for patients in hospital, with those discharged returning as outpatients. Patients were classified according to Functional Independent Measure (FIM) gait categories. Gait category of FIM was utilized to assess the functional status of patients at physical examination. These assessments were performed by a single trained trial coordinator who was blinded to patient demographics, stroke subtype, stroke severity and Doppler results. The Modified Ashworth Scale (MAS)[20] was scored as a clinical measure of spasticity during sitting, with the hemiparetic side calf muscles in an extended knee position.

Statistical analysis

All analyses were performed using Microsoft Office Excel 2007 and Excel statistical software (SSRI, Tokyo). The χ^2 test and Mann-Whitney U test were applied for statistical analyses. Statistical significance was set at a level of $p<0.05$. Multiple logistic regressions were performed using Excel statistical software with clinical features as independent variables, and the presence or absence of DVT as the dependent variable. Variables studied were: age; gender; SIAS score (grade 0 to 5); MAS (grade 0 to 4); gait FIM (grade 1 to 7); and previous treatment with aspirin, ticlopidine, cilostazol or warfarin. An alpha level of 0.05 was considered significant.

Results

Twenty-four patients were excluded from analysis because of exclusion criteria. Data from 272 patients were thus included in the analysis. Physical examination was performed at a mean of 89.5 days (median, 98 days; range, 32-345 days) after stroke onset. Table 1 shows baseline characteristics of the 272 eligible patients (demographics, stroke type, lower limb paresis, spasticity and gait ability with and without DVT). All patients were on antiplatelet or anticoagulant therapy unless contra-indicated. To assess the consistency with which medications prescribed on transfer to rehabilitation were continued unchanged during the rehabilitation hospital stay and outpatient clinic. A total of 54 patients were symptomatic and/or had D-dimer >0.5 µg on examination for DVT at the time of Doppler scans among the 272 patients; initially eligible. Asymmetry in calf and/or thigh measurements was a particularly important clinical sign. DVT was documented in 24 patients (8.8%) undergoing rehabilitation. Twenty-one distal and 3 proximal DVT of the patients who underwent Doppler study were found on

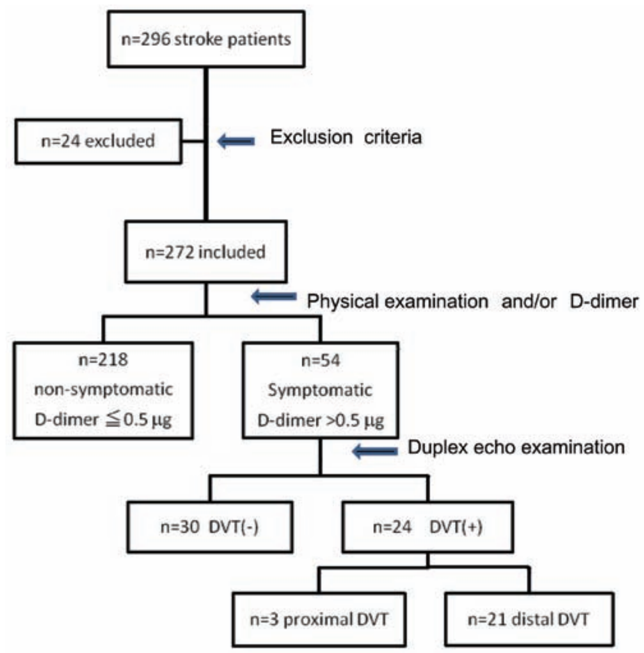

Fig. 1 Patients flow chart

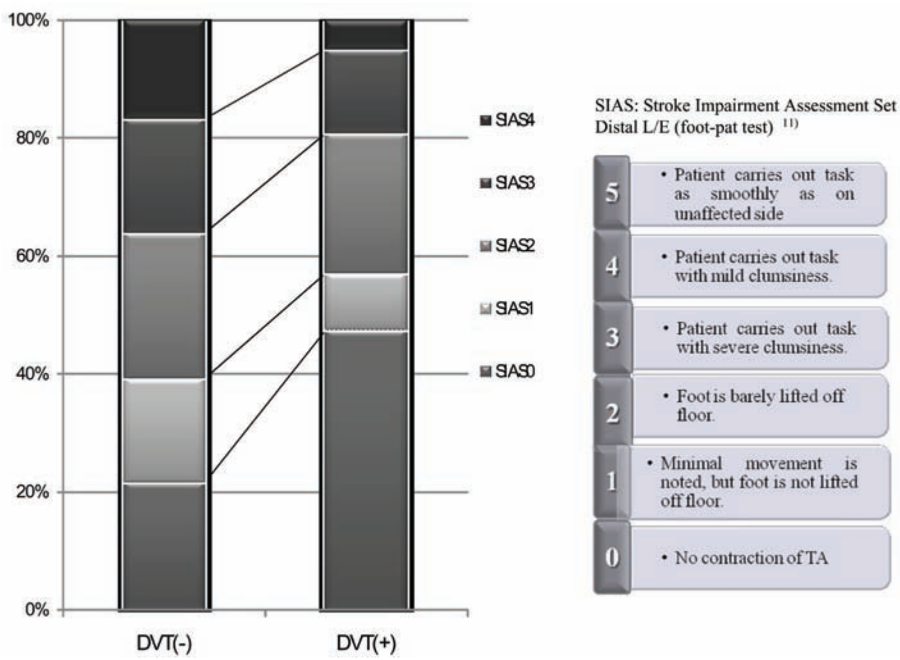

Fig. 2 Lower extremity hemiparesis (distal SIAS) and DVT. A significant association existed between occurrence of DVT and more severe lower limb paresis as measured by SIAS score (p<0.05: Mann-Whitney U-test).

the hemiparetic side (Fig. 1). Bilateral DVT was present in 3 of these patients. DVT was diagnosed at a mean of 233 days (median, 222 days; range, 66-345 days) after stroke onset.

Patients who had DVT did not differ significantly from those without DVT in terms of age or sex. No association was seen between occurrence of DVT with infarction type and presence of large stroke. Median SIAS of lower extremity SIAS of lower extremity hemiparesis was 3 (hip), 3 (knee), 1 (ankle) for patients with DVT and 3 (hip), 3 (knee), 2 (ankle) for patients without DVT. Ninety-four percent of the patients in whom asymmetry in calf and/or thigh measurements exceeded 2.5 cm were diagnosed as having DVT according to Doppler study. A significant association was seen between occurrence of DVT and more severe ankle joint paresis as measured by SIAS ankle score ($p<0.05$, Mann-Whitney U test) (Fig. 2). There was no significant association between DVT and SIAS hip or knee scores. Median FIM gait was 4 for both patients with and without DVT. However, FIM gait score was significantly lower for patients with DVT than for patients without DVT ($p<0.05$, Mann-Whitney U test) (Fig. 3). Median MAS of calf muscles was 2 for patients with DVT and 1 for patients without DVT. Ankle MAS score was significantly higher for patients with DVT than for patients without DVT ($p<0.001$, Mann-Whitney U test) (Fig. 4). A significantly higher proportion of patients with DVT used klenzac or plastic ankle-foot orthosis (AFO), when compared with patients without DVT ($p<0.05$, χ^2 test) (Fig. 5). DVT was seen in 17 patients with aspirin, 7 patients with ticlopidine and 2 patients with warfarin. No patient with cilostazol suffered DVT in this study (Fig. 6).

Multiple logistic regression analysis using age, sex, stroke type, SIAS (hip, knee and ankle), MAS, gait FIM score, need for orthosis, antiplatelet drugs and anticoagulant drug as variables showed only spasticity (MAS) and cilostazol as independently associated with presence of DVT. A significant increase in development of DVT was associated with severe spasticity in hemiparetic calf muscles (odds ratio (OR) 28.2; 95% confidence interval (CI), 6.9-113.5). No significant increase in DVT was associated with age (OR 1.046; 95% CI, 0.981-1.116), sex (OR 1.461; 95% CI, 0.335-6.387), stroke type (OR 1.709; 95% CI, 0.463-6.306), SIAS hip (OR 1.286; 95% CI, 0.077-21.539), SIAS knee (OR 2.630; 95% CI, 0.158-43.891), SIAS ankle (OR 0.630; 95% CI, 0.239-1.660), gait FIM score (OR 2.197; 95% CI, 0.774-6.236) or use of AFO (OR 0.878; 95% CI, 0.313-2.465). Only use of cilostazol (OR <0.001; 95% CI, <0.001 to >999.9) showed a significant protective effect against VTE risk. Neither warfarin (OR 0.686; 95% CI, 0.054-8.779) nor any other antiplatelet agents (aspirin (OR 4.892; 95% CI, 0.382-62.716), ticlopidine (OR 3.469; 95% CI, 0.235-51.208)) reached statistical significance in multiple logistic regression analysis.

Three patients were on heparin infusion after diagnosis of proximal DVT. One individual with proximal DVT

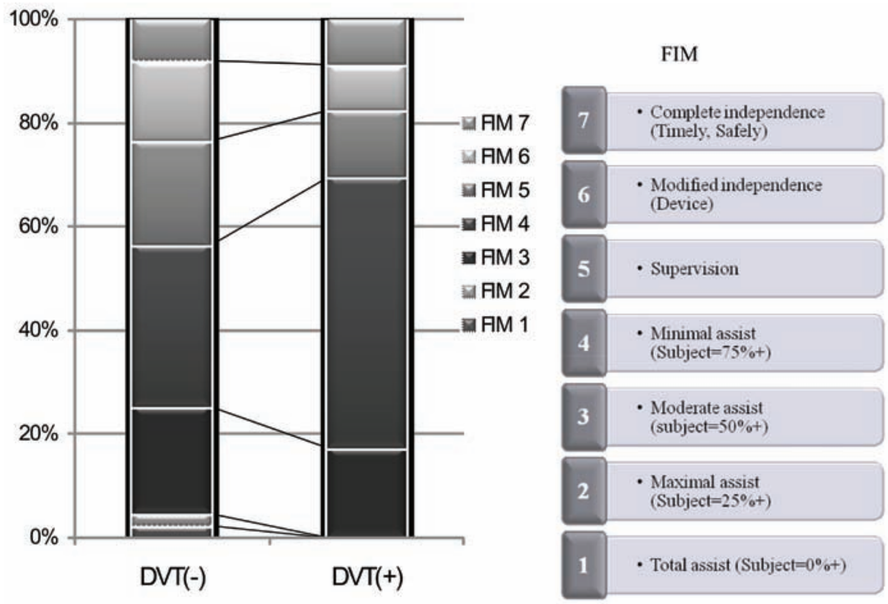

Fig. 3 Gait FIM and DVT. FIM gait score was significantly lower for patients with DVT than for patients without DVT ($p<0.05$: Mann-Whitney U test).

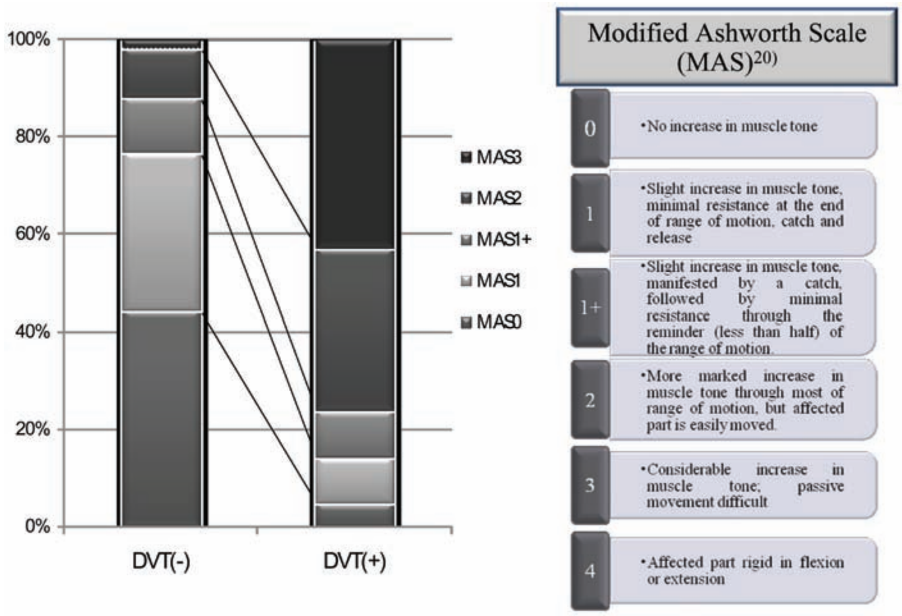

Fig. 4 Calf muscles spasticity (MAS) and DVT. Ankle joint MAS was significantly higher for patients with DVT than for patients without DVT ($p<0.001$, Mann-Whitney U test).

displayed symptomatic PE, confirmed on spiral CT of the thorax, which was treated with anticoagulation and oxygen supplementation and resolved completely. One patient, who had a filter in place for treatment of early venous thromboembolism, developed recurrent venous thromboembolism during rehabilitation.

Discussion

Patients undergoing in- or outpatient rehabilitation are at increased risk for DVT, but accurate diagnosis of DVT by clinical examination is reportedly complicated and frequently unreliable. In contrast, recent attempts to de-

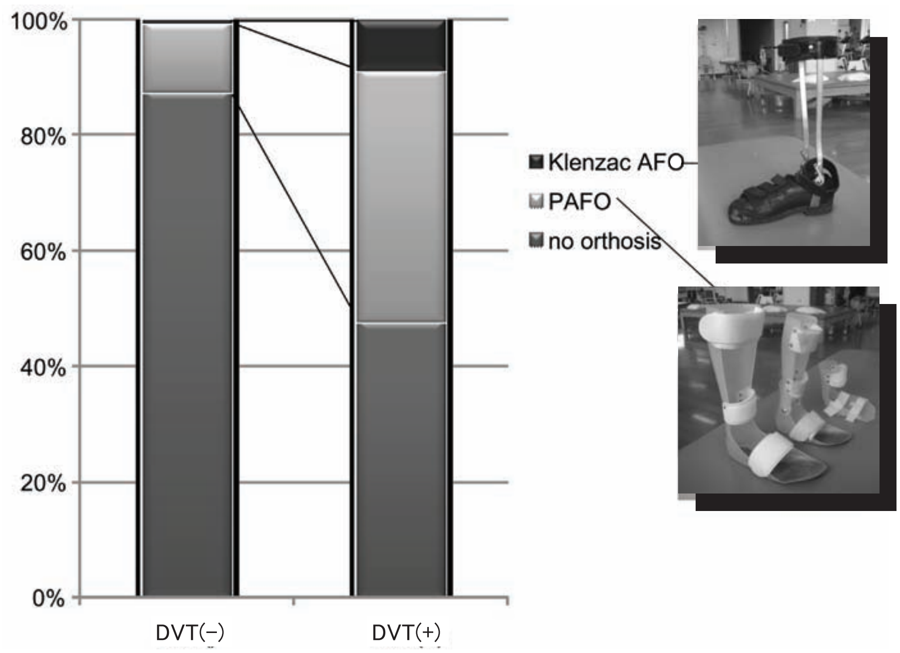

Fig. 5 Orthosis and DVT. A significantly higher proportion of patients with DVT used AFO, when compared with patients without DVT ($p<0.05$, χ^2test).

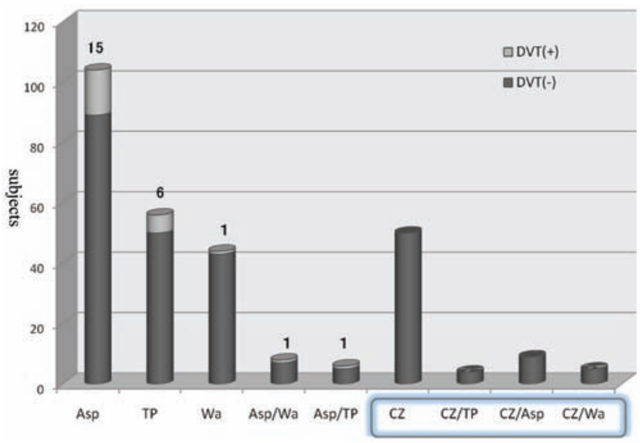

Fig. 6 Antiplatelet, anticoagulant drugs and DVT. (Asp, Aspirin; TP, Ticlopidine; CZ, Cilostazol; Wa, Warfarin) Numbers inside the graph show the number of subjects with DVT among subjects receiving each drug.

lineate clinical signs of DVT have proven more successful. A recent study found swelling, immobility and fever to be associated with DVT confirmed by venography. Sioson[6] reported that profound weakness, male gender, interval between stroke onset and DVT examination, edema and hyperpigmentation were independently associated with positive DVT in patients admitted to a rehabilitation hospital. Diamond[13] demonstrated the ability of certain subspecialists to diagnose DVT by clinical examination. Specificity of clinical diagnosis is low, as the symptoms and signs can all be caused by nonthrombotic disorders. Nevertheless, clinical findings are an important, if not crucial, adjunct to objective diagnostic testing. Since pretest probability plays a pivotal role in test selection and interpretation, a well-recorded history and careful physical examination are crucial parts of the diagnostic pathway. It should be kept in mind as a screening test that difference of calf diameter is an important sign for ruling in DVT among clinical signs, while absence of calf swelling or a difference in calf diameter is useful for ruling out DVT.[14] Individual clinical features are of limited value in diagnosing DVT and overall assessment of clinical signs is useful for diagnosis of DVT as a screening test.[14] Therefore, we adopted overall assessment of clinical signs as a screening test at first. These clinical features often increased gait disturbance of stroke patients in this study. As a noninvasive method for diagnosis of DVT, venous ultrasonography (compression ultrasonography with or without Doppler flow assessment) has been extensively evaluated and widely used. In symptomatic patients with suspected first episode of DVT, clinical assessment and D-dimer testing are complementary to testing with venous ultrasonography and impedance plethysmography.[21]

Most DVT patients displayed distal type in this study. Among the crural veins, the soleal vein is particularly important as an initial site of DVT. The detection rate of

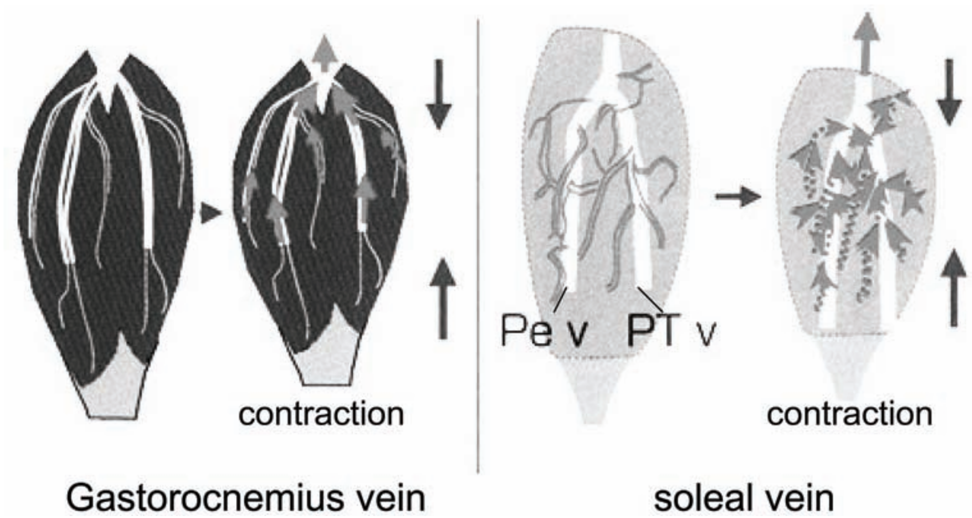

Fig. 7 Venous flow pattern with muscle contraction of gastrocnemius and soleal vein[28]
PTv: posterior tibial vein, Pev: Peronal vein. In gastrocnemius muscle the venous blood return flows from distal to proximal portion with muscle contraction as the muscle pomp. On the other hand, in soleal muscle the venous blood flows to various directions with muscle contraction because of the mesh-like venous structure and soleal muscle hyper tone might induce the stagnation of venous flow.

thrombi in the soleal vein has been reported to be highest, at 90%.[22] Management of calf vein DVT has also been controversial. While it is well established that calf vein DVT rarely causes pulmonary embolism, some argue that the propensity to propagate into proximal veins and become both symptomatic and a potential source of embolus warrants formal anticoagulation.[7] Distal (calf) DVT poses a low risk for embolization, in contrast to the high risk with proximal (thigh) thrombi.[23] Proximal venous thrombosis requires antithrombotic therapy. With deep venous thrombosis confined to the calf, serial noninvasive testing is safe to perform, with antithrombotic therapy used only for patients in whom thrombus subsequently extends into the thigh. Whether therapeutic anticoagulation is superior to heparin prophylaxis in the prevention of DVT has been impossible to determine. Use of warfarin at a fixed low dose (2 mg) has been associated with a non-significant reduction in any DVT, proximal and clinically detected DVT, but not with any bleeding complications.[24] Stroke patients without reduced mobility, usually related to lower limb paresis, should not be routinely given low-dose anticoagulants, as the DVT or PE risk is probably very low and bleeding complications may still occur.[25]

Virchow postulated that 3 factors would be of fundamental importance: 1) vessel wall damage; 2) blood flow changes; and 3) alterations in the blood. However, venous stasis alone was insufficient to produce thrombus, as thrombus would form when venous stasis was combined with either vessel wall damage or increased blood coagulability.[26] Oczkowski[7] *et al*, reported that the incidence of DVT is greatest in bedridden or wheelchair-bound patients undergoing stroke rehabilitation. Age and degree of weakness are significantly associated with presence of DVT at the subacute phase. A stepwise increase in risk of DVT may be seen with more severe neurological impairment, as with this study result. Stroke patients have anatomical brain injuries and more medical complications after stroke that may contribute to an acute inflammatory state and an increase in haemostatic factors with a propensity for thrombosis.[27] The reason for a high frequency of soleal vein thrombosis is that the soleal vein and soleal muscle are anatomically weak and susceptible to exposure to venous stagnation caused by prolonged sitting.[22] As the veins in soleal muscles anatomically run like a random mesh not along the muscle fiber,[28] the venous flow is easy to be disturbed by the excessive contraction of the soleal muscle (Fig. 7). Increased soleal muscle tone could induce blood pooling in the intramuscular venous sinuses with the incompetent muscle pump because of the specific venous structure in soleal veins. Additionally the calf muscle spasticity could decrease the ankle joint range of movement which disturbs the function of calf muscle venous pump. This might be the reason why spasticity (MAS) was significantly associated with presence of DVT. It is likely that vessel wall damage might be encountered in hemiparetic patients with external compression from an AFO on the calf during gait and standing. In the rehabilitation phase of stroke patients, combined effects on a calf muscle with spasticity and AFOs compression could induce hemostasis, leading to vein wall distension with endothelial damage, and metabolic damage to the endothelial lining. Little information is available, however, regarding the association between DVT with orthotic devices commonly used in stroke patients. Kroll *et al*[29] reported a unique case in which the use of bilateral plastic AFOs (PAFOs) was associated with calf DVTs in a patient with chronic inflammatory demyelinating polyradiculoneuropathy. A lack of ankle joint movement reduces muscle pump action and is likely to result in decreased resilience of muscle tissue to pressure from the calf support of AFOs. This pressure is therefore more likely to compress the veins and impair venous return.[29] Most of DVT patients with AFO complaint pain and tightness in the posterior aspect of hemiparetic calf with the dent at the upper calf muscle potion due to AFO upper edge in this study. Using AFOs for extreme calf muscle spasticity might induce endothelial injury and thrombosis in the calf veins with hypercompression. Though the use of AFO is generally useful rehabilitation intervention, medical stuff should check the extreme calf compression with AFO which could contribute to distal DVT. The main factors inducing DVT among stroke patients would differ depending on the stroke phase, as severe paralysis and immobility are present in the acute phase, whereas the combination of disability and vein injuries is seen in rehabilitation and chronic phases. External compression factors such as AFOs may compound the problems of muscle weakness and immobility and cause calf thrombus. Recent study also reported that minor injuries in the leg are associated with greater risk of DVT.[30]

Andre *et al*[31] and Rodgers *et al*[32] reported the possible role of aspirin as a modest DVT preventive strategy from meta-analysis data. The frequency of DVT in acute stroke is reduced by anticoagulants, but not by antiplatelet agents.[17] Harvey *et al*[10] also reported that aspirin seemed ineffective in a large retrospective study of patients undergoing rehabilitation for stroke. Aspirin is the most popular drug to reduce mortality and recurrence of cerebral infarction, but has not seemed to significantly reduce the rates of DVT or PE.[33–35] Although suppression of platelet-leukocyte aggregate formation was comparable between aspirin and cilostazol, cilostazol has the protective effects of endothelial cells with swelling and roughness of the surface from activated leukocytes rolling and adhesion.[36] Such protective effects on the endothelium by cilostazol could reduce vein microinjury induced with spasticity and orthosis compression following DVT.

In conclusion, incidence of DVT in the rehabilitation phase following stroke was not low (8.8%) and DVTs were predominantly distal DVT on the hemiparetic side. A significant association was seen between occurrence of DVT and more severe lower limb paresis as gait disturbance. In particular, higher incidences of DVT were associated with severe calf muscle spasticity and use of AFO. Micro-injuries in the venous endothelium due to spasticity and AFO might cause DVT. Cilostazol seems effective for protecting against venous endothelial damage following DVT.

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