

ORIGINAL ARTICLES

Venous thromboembolism in ischaemic stroke in Asia

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Abstract

Background: There are extensive studies indicating that deep venous thrombosis and pulmonary embolism contributes to significant morbidity and mortality after acute ischaemic stroke in the West, with established guidelines for prophylaxis. The situation is less clear in Asia. Accordingly, a literature search was performed to review the available evidence. **Methods:** A search was performed with all published materials in PubMed, Directory of Open Access Journals and BioMed Central, using the following keywords “venous thromboembolism”, “Asia”, “stroke”, “deep venous thrombosis” and “pulmonary embolism”. Systematic and non-systematic studies, previous review articles with their related references were also reviewed. **Results:** Wide ranging prevalence of venous thromboembolism has been reported after acute ischaemic stroke in Asia, 1% or less in clinical studies, 4.8% to 45% with imaging studies. The prevalence is lower as compared to Caucasian populations, 1.5% to 5.6% in clinical studies, 11% to 80% with imaging studies.

Conclusion: The problem of venous thromboembolism is not negligible in Asia. There is a need for future studies in Asia with larger sample sizes. Antiplatelet drugs should be routinely used as prophylaxis while compression stockings applied for those with significant limb weakness. Prophylactic anticoagulation may be considered in those with additional risk factors.

INTRODUCTION

A review of the evidence available for venous thromboembolism after acute ischaemic stroke in Asian patients have not been performed to date despite the continuing controversy that venous thromboembolism in stroke patients was less frequent among Asians compared to Caucasians. Accordingly, this review aims to assemble and interpret the accumulated evidence of venous thromboembolism among stroke patients in Asia, compare the current evidence with the Western literature on the background of recent therapeutic trials and to make clinical recommendations.

Previous studies have suggested that venous thromboembolism in stroke patients was likely to be less frequent among Asians compared to Caucasians. Evidence for this came indirectly from various studies. A comparative study within multi-ethnic California revealed that the risk ratio for annual venous thromboembolism for Asians was 0.2 compared with Caucasians.¹ Autopsy studies were also noted to be lower in Japanese (0.7%) compared with North Americans (15%).² The annual incidence of venous thromboembolism in Hong Kong Chinese was estimated at 16.6

events per 100,000 population. This incidence was 10 to 20% of the rates found in Western populations.³ In addition, other studies in Asia noted that venous thromboembolism incidence in multi-ethnic Singapore among hospitalized patients was 15.8 per 10,000 admissions⁴ while its prevalence in post operative conditions in Malaysia and Singapore such as hip surgery⁵, colorectal surgery⁶, cranial procedures⁷ and general surgery⁸ were 14%, 3%, 5% and 2.2% respectively. A previous review in Asia⁹ noted a similar wide ranging prevalence in post-operative settings with ranges between 3%-63%. Overall, these rates were lower compared with Western data, which routinely showed prevalence of between 28-80% in similar clinical situations. However, no previous critical evaluation has been performed among stroke patients in Asia and to our knowledge, this is the first of such a review.

METHODS

A retrospective review from 1970 to June 2008 was performed on all published material listed in PubMed, Directory of Open Access Journals

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and BioMed Central. Keywords in the search were “deep venous thrombosis”, “ pulmonary embolism”, “venous thromboembolism”, “stroke”, “Asia” and individual countries in Asia, i.e. “Thailand”, “China” and so forth. Another search was made without the countries and this revealed all publications to date including published reports globally. All relevant papers and related references from the primary papers were reviewed but due to a paucity of studies on intracerebral haemorrhage and related venous thromboembolism, this type of stroke was excluded. Data abstracted from the papers included nature of the study, year, country, imaging modalities performed, prevalence of venous thromboembolism (deep vein thrombosis and pulmonary embolism) and sample size of the study. All studies prospective or retrospective were included. The studies were classified into Western or Asian populations and analyzed.

RESULTS

All relevant information was abstracted from every published report found. Nine studies¹⁰⁻¹⁹ were identified within the Asian population.

These were published in 1980 to 2008. The total number of patients from the pooled studies was 17,086. The prevalence range was 0.5% to 45%. A comprehensive list of 19 studies²⁰⁻³⁸ on predominantly Caucasian populations was published from 1972 to 2004 and covered numerous well organised but rather small therapeutic trials. The prevalence range was 1.6% to 80% with a pooled patient sample size of 3,040 patients. The data obtained were summarized in Table 1 and 2.

DISCUSSION

Epidemiology of post-stroke venous thromboembolism: Comparison between East and West

The first study in Asia after acute stroke was performed by Tso *et al* in 1980.¹⁹ This study was conducted on 35 Chinese stroke patients and found that the prevalence of deep vein thrombosis was 17%. The imaging modality was ¹²⁵I-fibrinogen scanning which is now obsolete. There was a paucity of studies until the mid-1990s where large

Table 1: Prevalence of venous thromboembolism in Asian post-stroke patients

Author and country	Year	Prevalence in percent	No. of patients	Method of investigation
Navarro <i>et al</i> ¹⁰ (10 Asian countries)	2008	0.5	1,013	Clinical
Tan <i>et al</i> ¹¹ (Singapore)	2007	4.8	44	Ultrasound
de Silva <i>et al</i> ¹² (Singapore)	2006	45	111	Ultrasound
Sun <i>et al</i> ^{13,14} (China)	2004	21.7	488	Ultrasound
Tongiputn <i>et al</i> ¹⁵ (Thailand)	1999	6.3	111	Ultrasound
International Stroke Trial Collaborative Group ¹⁶ (China)	1997	0.9	4,859	Clinical
Chinese Acute Stroke Trial ¹⁷ (China)	1997	0.2	10,320	Clinical
Kay <i>et al</i> ¹⁸ (Hong Kong)	1995	1.0	105	Clinical
Tso ¹⁹ (Hong Kong)	1980	17	35	¹²⁵ I-fibrinogen

Table 2: Prevalence of venous thromboembolism in stroke patients in Western populations

Author and country	Year	Prevalence in percent	No. of patients	Method of investigation
Kelly <i>et al</i> ²⁰ (United Kingdom)	2004	40	102	Magnetic resonance direct thrombin imaging
TOAST study group ²¹ (USA)	1998	1.6	628	Clinical
Hommel <i>et al</i> ²² (France)	1998	5.6	250	Clinical
Kwieceński <i>et al</i> ²³ (Poland)	1995	5.2	58	Clinical
Pambianco <i>et al</i> ²⁴ (USA)	1995	21	508	Ultrasound
Noel <i>et al</i> ²⁵ (Belgium)	1991	10.4	539	Venography
Oczkowski <i>et al</i> ²⁶ (Canada)	1992	11	150	Impedance plethysmography
Elias <i>et al</i> ²⁷ (France)	1990	80	15	¹²⁵ I-fibrinogen
Sandset <i>et al</i> ²⁸ (Norway)	1990	34	50	Venography
Prins <i>et al</i> ²⁹ (Netherlands)	1989	50	30	¹²⁵ I-fibrinogen
Sioson <i>et al</i> ³⁰ (USA)	1988	33	105	Impedance Plethysmography
Turpie <i>et al</i> ³¹ (USA)	1987	28	25	¹²⁵ I-fibrinogen
McCarthy & Turner ³² (UK)	1986	73	73	¹²⁵ I-fibrinogen
Miyamota <i>et al</i> ³³ (USA)	1980	29	150	¹²⁵ I-fibrinogen
McCarthy <i>et al</i> ³⁴ (USA)	1977	16	75	¹²⁵ I-fibrinogen
Gibberd <i>et al</i> ³⁵ (England)	1976	50	26	¹²⁵ I-fibrinogen
Warlow <i>et al</i> ³⁶ (Scotland)	1976	53	76	¹²⁵ I-fibrinogen
Cope <i>et al</i> ³⁷ (England)	1973	33	150	Ascending venography
Warlow <i>et al</i> ³⁸ (Scotland)	1972	60	30	¹²⁵ I-fibrinogen

clinical studies documented a low prevalence of clinical venous thromboembolism with prevalence of 0.2-1%.¹⁶⁻¹⁸ Recent studies also noted the low prevalence of venous thromboembolism, in the range of 0.5% to 1% when clinical evaluation was employed¹⁰ while this was higher with the use of imaging technology, ranging from 6.3% to 45%.¹¹⁻¹⁵ This indicates that a large percentage of venous thrombosis was present sub-clinically or may have been missed due to lack of awareness or subsequent confirmatory investigations. These studies included stroke patients recruited from Singapore, China, Thailand, Hong Kong and from a large, multi-center, prospective clinical study on stroke complications in Asia.

A review of Western literature on post-stroke venous thromboembolism since systematic studies began in the 1970s revealed a high prevalence of venous thromboembolism after acute ischaemic stroke. The prevalence ranged from 11% to 80%.²⁰⁻³⁸ (Table 2). It was also interesting to note that the prevalence of venous thromboembolism has declined over the last 25 years. Studies from 1972 to 1990²⁷⁻³⁹ documented venous thromboembolism prevalence between 16-80%. Studies after 1990 showed the prevalence to be from 1.6% to 40%.²⁰⁻²⁶

In reviewing and interpreting these studies, several pertinent factors should be considered. Studies of venous thromboembolism in the 1970s should be regarded as studies of natural history of stroke. On the other hand, there is widespread use of anti-platelet therapy from the 1990s. A systematic study on antiplatelet therapy⁴⁰ by Sandercock *et al* concluded that antiplatelets reduced the rate of pulmonary embolism by 20%. Therefore, this may account for the higher prevalence of venous thromboembolism as complications from stroke noted in earlier studies before widespread use of antiplatelet therapy for many atherothrombotic diseases.

The second issue is the confounding factors in the West with predominantly Caucasian populations. It has been recognized that genetic polymorphisms such as factor V Leiden and prothrombin G20210A are common in the West. The presence of these genetic variants may predispose patients to venous thromboembolism following stroke and explain the higher prevalence in the Western populations. A recent study by Jun ZJ *et al*⁴¹ confirmed that these genetic polymorphisms were not found in Chinese populations. On the other hand, antithrombin III, protein C and protein S deficiencies⁴²⁻⁴⁵ have been reported in Asia. However, these conditions were usually diagnosed in the context of positive

family histories. Therefore, the genetic risk factor profile for venous thromboembolism is likely to be different in the Asian populations.

The third issue is the use of different imaging modalities which have evolved over time. The different sensitivities, specificities and invasiveness of older techniques (venography, impedance plethysmography and ¹²⁵I-fibrinogen) limit the usefulness of a body of previous literature. These techniques being more invasive also limit the sample size and confidence intervals of data obtained. In addition, many early studies failed to distinguish proximal deep venous thrombosis, which is clinically more significant, from distal disease.

In summary, there is evidence that the prevalence of venous thromboembolism has decreased over the last two decades and this can be partly explained by the wide-spread use of anti-platelet therapy. There is evidence that Asians have a lower prevalence of venous thromboembolism after stroke and this finding is also consistent with the lower prevalence of venous thromboembolism after surgery. The wide ranging prevalence in many studies from Asia and elsewhere is related to the measurement of outcome ie clinical or sub-clinical venous thromboembolism as well as the imaging modality used.

Clinical guidelines in stroke

To our knowledge, there are no clinical recommendations on venous thromboembolism prophylaxis following acute stroke in clinical practice guidelines on stroke and transient ischemic attacks published in Asia. However, the European Stroke Organization⁴⁶ recommended that aspirin should be used while prophylactic anticoagulation with low dose subcutaneous unfractionated heparin or low-molecular-weight heparin should be considered for patients at high risk for venous thromboembolism. Compression stockings should also be used in stroke patients with weak or paralyzed legs while early mobilization and optimal hydration should be maintained. The Royal College of Physicians of London⁴⁷ also recommended a similar approach towards prevention of venous thromboembolism after acute ischemic stroke.

Despite the body of evidence, a recent multi-center cross-sectional observation study⁴⁸ revealed inadequate venous thromboembolism prophylaxis in a large cohort of stroke patients in China. The situation is also true globally⁴⁹ as seen in a recent study, not only in post-acute stroke care but across

a spectrum of medical patients.

While it has been well recognized that the risk of deep vein thrombosis in acute stroke correlated with the degree of paralysis⁵⁰, advanced age⁵¹ and atrial fibrillation⁵², routine prophylactic anticoagulation has not been widely used due to the fear of possible bleeding complications after stroke. In the International Stroke Trial (IST)¹⁶ performed in China, subcutaneous unfractionated heparin initiated within 48 hours of ischaemic stroke and continued for 2 weeks was compared to a control group without heparin. There was a reduction of thromboembolism and recurrent stroke with an increased risk of hemorrhagic transformation and extracranial hemorrhage. On the other hand, a previous systematic review which evaluated 7 related studies in Caucasian populations noted similar effectiveness of prophylactic unfractionated heparin but with no evidence of increased bleeding.⁵³

The slight superiority of low-molecular-weight heparin over unfractionated heparin was shown in a recent randomized controlled trial involving Caucasian populations with lower rates of distal to proximal deep vein thrombosis propagation, confirmed by ultrasound.⁵⁴ However, pulmonary embolism rates were unchanged between both groups. Previous systematic reviews of low-molecular-weight heparin trials against unfractionated heparin have shown non-significant trends for reduction of pulmonary embolism and deep vein thrombosis. Improved safety has also not been conclusively demonstrated.⁵⁵⁻⁵⁶

In systematic review of studies comparing aspirin and low molecular weight heparin for prevention of stroke recurrence, a significant reduction in symptomatic venous thromboembolism was noted in the low molecular-weight heparin group but this was complicated by a rise in major extracranial bleeding.⁵⁷⁻⁵⁸ A recent study on Chinese patients with symptomatic intracranial large artery occlusive disease, comparing low molecular weight heparin and aspirin demonstrated no evidence of definite clinical advantage from either agents but with significant bleeding complications in the low-molecular-weight heparin treatment arm.⁵⁹

In summary, this is a review of epidemiological data on the prevalence of clinical and sub-clinical venous thromboembolism after acute stroke from Asian and Western populations using different diagnostic modalities.⁶⁰ There is substantial evidence that venous thromboembolism after stroke is also a significant problem in Asia with prevalence ranging from 0.5-45%. There is also

evidence of an important gap in prophylactic anticoagulation.

Risk and benefits should be considered in the decision for venous thromboembolism prophylaxis with anticoagulants after a recent ischaemic stroke. There is substantial evidence that post stroke patients should not have routine prophylactic anticoagulation due to possible bleeding complications.^{16,57-59} One approach is to initiate hospital-wide venous thromboembolism risk assessment strategies and utilize prophylactic anticoagulation in the presence of additional risk factors such as obesity, malignancy, previous documented deep venous thrombosis, family history and prolonged immobility. The patients may be given unfractionated heparin at 5,000 units twice daily or 5,000 units three times daily in heavier patients. Alternatively, low-molecular-weight heparin at the lowest prophylactic dosage can be given. In addition, compression stockings should be used whenever possible in stroke patients with significant lower limb weakness. Hydration with early mobilization should be optimized whenever possible.

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