Asian Cerebral Venous Thrombosis Registry: Study Protocol

Abstract

Introduction: Cerebral venous thrombosis (CVT) is a well known but poorly reported entity. Most of the studies and registries related to CVT are reported from European countries. No large multi-center or multi- national data base or registry has been reported from Asian countries. CVT is not uncommon in Asia especially in south Asian subcontinent including India, Pakistan and Bangladesh. One study reported from India that CVT accounted for half of all strokes in the young and 40% of strokes in women. Review of CVT cases from Asian countries is suggestive of differences in risk factors profile and outcome in these patients as compared with European studies. These findings from multi- center data base in Asian countries will be extremely important in identifying risk factors for CVT in these countries.

Study design: This is a prospective observational study. We plan to enroll more than 1000 patients from at least ten Asian countries (about 40-50 centers). Patients will be enrolled prospectively and followed for six months. Primary outcome would be death or dependence as assessed by modified Rankin scale (mRS). Data will be collected on a pre-defined data form. There will not be any laboratory test, investigation or treatment specified by the study. Only results of routinely performed studies and treatments will be recorded. Patient (aged 16 or above) will only be included in study if they have diagnosis of CVT proven by magnetic resonance imaging (MRI), magnetic resonance venography (MRV), computed tomography (CT) venography and cerebral venography according to established criteria. Follow up visits will be performed at 6 months, 12 months, and yearly thereafter, preferably by direct interview and observations by the local investigators.

Outcome: Primary outcome is death or dependence (mRS >2) at the end of the follow-up period. Secondary outcomes are death and dependence at 6 months. Patients will be enrolled from January 2009 to June 2010.

Keywords: Cerebral venous thrombosis, Asian, multi-center, registry, prospective

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Abbreviations: CVT, Cerebral venous thrombosis; **MRA**, magnetic resonance angiography; MRV, Magnetic Resonance Venography: **CT**, computed tomography; **CTA**, computed tomographic angiography;

Background:

Cerebral venous thrombosis (CVT) is a well known but poorly reported entity. The largest data base of these patients included 624 patients.[1] Most of the studies and registries related to CVT are reported from European countries. No large multi-center or multi- national data base or registry reported data from Asian countries. CVT is not uncommon in Asia especially in south Asian subcontinent including India, Pakistan and Bangladesh. Pangayara reported that CVT in India accounted for half of all strokes in the young and 40% of strokes in women.[2] Review of CVT cases from Asian countries is suggestive of differences in risk factors profile and outcome in these patients as compared to European studies. Largest cohort of CVT patients from Europe (n=624) reported that 50% of these cases were related to oral contraceptive pills (OCP), 6% were due to pregnancy, and 14% were secondary to puerperium.

A study of 182 adult patients with CVT from USA reported 7% were due to pregnancy and puerperium, and 5% related to OCP use.[3] A study from Pakistan (n=109) patients with CVT reported that 17% were due to pregnancy and puerperium and 5% related to OCP use.[4] Cantu from Mexico reported 59% cases due to pregnancy/ puerperium.[5]

These findings from multi- center data base in Asian countries will be extremely important in identifying risk factors for CVT in these countries. The registry will help planning future case-control studies and randomized- controlled trials related to CVT.

Objectives:

To identify risk factors, presentation and outcome of CVT patients in Asian patients.

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Design: Prospective observational study
Duration: Enrollment period 18 months. Follow up at least six months

Methods:

We plan to enroll more than 1000 patients from various Asian countries. Patients will be enrolled prospectively and followed for six months. Primary outcome would be death or dependence as assessed by modified Rankin scale (mRS). Data will be collected on a pre-defined data form. No laboratory test, investigation or treatment is mandated by the study. Only results of routinely done studies and treatments will be recorded without any specific investigations or treatment performed for purpose of study alone.

Inclusion Criteria:
1. Patient will only be included in study if they have diagnosis of CVT proven by MRI, MRV, CT venography and cerebral venography according to established criteria.
2. Age 16 years or above

Exclusion Criteria:
Age less than 16 years

Consent:
Patients will be included in the study after signing an informed consent form. Investigator of the participating center will be responsible for obtaining informed consent. There will be a separate consent form for each center available in local language.

Imaging, Demographic and Clinical Data, Risk Factors and Treatment:

Following information will be recorded: demographic data; dates of onset of symptoms, of hospital admission and of confirmation of the diagnosis by imaging symptoms and signs from onset and diagnosis, Glasgow coma scale (GCS) score on admission and during the clinical course; National Institutes of Health (NIH) stroke scale at admission, imaging methods used; location of the thrombus; and number, location and size of any parenchymal lesions.

A list of potential risk factors for CVT is attached to the inclusion form to assist investigators with the etiological work up; thrombophilia screening (proteins C and S, anti thrombin III lupus anticoagulant, anticardiolipin antibodies, factor V Leiden. and G20210A mutations) are recommended. The choice of treatment will be left to the treating physician, but all treatments will be systematically recorded.

Data Collection:
All patients with diagnosis of CVT at participating centers will be enrolled. The clinical data will be collected by a physician. All CT scans and MRIs will be read by a trained radiologist. Patients will be enrolled after radiological confirmation of CVT.

The data regarding laboratory tests and radiological investigations will be retrieved through medical records of patients. The data regarding neurological examination for stroke, severity and disability scores will be collected by serial evaluations by investigator or other physicians.

Follow-Up:
Follow up visits will be performed at 6 months, 12 months, and yearly thereafter, preferably by direct interview and observations by the local investigators. If such evaluation is not possible, alternative methods including telephone interview of the patient or interview of the relative or general practitioner. For patients who were lost to follow-up, the condition on the day of hospital discharge will be regarded as the final follow-up. Follow-up data recorded will be as follows: disability according to mRS, death, recurrent symptomatic sinus thrombosis (new symptoms with new thrombus on repeated venogram or MRI), other thrombotic events, seizure, headaches requiring bed rest or hospital admissions, severe visual loss (quantified with an optometric chart as ‹4/10), pregnancy, abortion and current antithrombotic and other treatments.

Outcome:
Outcome will be classified according to the mRS as complete recovery (mRS 0 to 1) partial recovery, independent (mRS ≤2), dependent (mRS 3 to 5) and death (mRS 6). For patients who have a telephone follow up the mRS score will be assessed by 3 previously validate questions. Primary outcome is death or dependency (mRS ›2) at the end of the follow-up period. Secondary outcomes are death and dependence at 6 months. For patients who missed the 6 month evaluation but have the 1 year follow-up, the "worst Rankin" scenario will be used. The mRS score either at discharge or at 1 year follow up (which ever is worse) will be used to estimate disability at 6 months.

Data Submission:
Data submission will be on line and paper submission. Each participating center will be provided with ID and Passwords for electronic data entry.

Imaging Analysis:
Central imaging analysis will be optional.

Duration Of Study:
Patients will be enrolled from January 2009 to June 2010. We plan to conclude study the in October 2010.

Statistical Analysis:
We will consider demographic, clinical and imaging variables and risk factors as possible explanatory variables of the outcomes. Bivariate analysis will be performed for each outcome with the X2 test (with Yates correction when necessary). Fisher exact test for categorical data and with the Student t test or ANOVA for continuous data will be used. Variables associated ($P<0.01$) with outcomes in the bivariate analysis will be entered into a multivariate analysis.

For the outcome of death or dependence at the end of follow up,

we will perform survival analysis using Kaplan-Meier and Cox regression statistics. We will calculate the hazard ratios (HRs) and 95% confidence intervals (CI) for the retained variables. For the remaining secondary outcomes, we will performed a logistic regression analysis (backward method) and calculate odds ratios (ORs) and 95% CIs for the retained varables. Data will be analyzed with SPSS 13.0 for windows.

Confidentiality:
The data will be accessible only by principal investigator. Data from one country will not be shared with a collaborators from another country. We do not plan to perform a country-wise data analysis. Patient's identity will not be exposed in any report or publication.

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