



**Karolinska
Institutet**

Department of Clinical Neuroscience

Intracerebral hemorrhage in patients treated with intravenous thrombolysis for acute ischemic stroke

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid
Karolinska Institutet offentligen försvaras i
Kugelbergsalen, Neurocentrum, Karolinska
Universitetssjukhuset, Solna

Fredagen den 12 september, 2014, kl 13.00

av

Michael V. Mazya

Leg. Läk.

Huvudhandledare:

Professor Nils Wahlgren
Institutionen för klinisk neurovetenskap
Karolinska Institutet

Bihandledare:

Docent Niaz Ahmed
Institutionen för klinisk neurovetenskap
Karolinska Institutet

Fakultetsopponent:

Professor Eric Jüttler
Department of Neurology
Universität Ulm, Germany

Betygsnämnd:

Professor Arne Lindgren
Institutionen för kliniska vetenskaper
Lunds Universitet

Professor Jan Malm
Institutionen för farmakologi
och klinisk neurovetenskap
Umeå Universitet

Docent Einar Eriksson
Institutionen för klinisk neurovetenskap
Karolinska Institutet

Stockholm 2014

ABSTRACT

Background. Nearly 30000 people suffer a stroke in Sweden every year. Stroke is the third most common cause of death after heart disease and cancer carrying a 17% mortality rate at three months. It is the most common cause of neurological disability in adults. Intravenous thrombolysis with alteplase is the only approved pharmacological therapy for acute ischemic stroke, improving neurological and functional outcome in one third of all treated patients. Meanwhile, thrombolytic treatment can in itself cause intracerebral hemorrhage. The aim of this thesis was to study risk factors associated with this complication, in a large cohort of ischemic stroke patients treated with intravenous alteplase.

Methods. All studies were based on patient data contained within the Safe Implementation of Treatments of Stroke - International Stroke Thrombolysis Register (SITS-ISTR). The main outcomes of interest were symptomatic intracerebral hemorrhage (SICH) by SITS-MOST, ECASS II and NINDS definitions, functional status at 3 months (modified Rankin Scale), and death at 7 days and 3 months.

Study 1. We aimed to develop a clinical scoring algorithm predicting the risk of SICH, using data from 31627 patients. Baseline and demographic factors associated with SICH were entered into a logistic regression model. Adjusted odds ratios (OR) were converted into points, summated to produce a risk score. We identified 9 predictors of SICH: stroke severity, plasma glucose, blood pressure, age, body weight, stroke onset to treatment time, aspirin or combined aspirin and clopidogrel, and history of hypertension. The overall rate of SICH was 1,8%. The score ranged from 0 to 12 points, showing a >70-fold increase in the rate of SICH for patients with a score ≥ 10 points (14,3%) compared to 0 points (0,2%), with an acceptable predictive performance, AUC-ROC = 0,70. We concluded that the SITS SICH Score is able to predict large thrombolysis-related SICH associated with severe clinical deterioration.

Study 2. The SEDAN score is another prediction algorithm for SICH. We assessed its predictive performance for two definitions of SICH. Odds ratios for SICH per one-point increase of the score were obtained using logistic regression. The predictive capability for SICH per ECASS II was moderate at AUC-ROC = 0,66. With rising scores, there was a moderate increase in risk for SICH ECASS II (OR 1,7 per point, $p < 0,001$), SICH rates between 1,6% for 0 points and 16,9% for ≥ 5 points. Prediction of SICH per SITS-MOST was weaker, AUC-ROC = 0,60, rates between 0,8% for 0 points and 5,4% for ≥ 5 points. We concluded that the predictive performance of the SEDAN was moderate for SICH per ECASS II and low for SICH per SITS-MOST.

Study 3. The European license for alteplase contraindicates its use in stroke patients treated with warfarin. Conversely, American guidelines accept it in patients with an international normalized ratio (INR) $\leq 1,7$. We studied the influence of warfarin on SICH, arterial recanalization, functional outcome and mortality in 768 patients with baseline warfarin treatment and $\text{INR} \leq 1,7$. They were older, had more comorbidities, and more severe strokes compared to patients without warfarin. There were no differences in SICH rates, mortality or functional outcome between warfarin and non-warfarin patients after adjustment for differences in age, stroke severity and co-morbidities. Arterial recanalization defined as the disappearance of a baseline hyperdense cerebral artery sign at 22-36 hour imaging was increased in warfarin patients at 63% vs 55%, $p = 0,022$.

Study 4. Hemorrhage following stroke thrombolysis can occur in brain parenchyma remote from acutely ischemic tissue (PHr), as well as in local relation to the infarct (PH). We investigated the risk factors, mortality and functional outcome in patients with the poorly understood complication of PHr, as well as PH, and concomitant occurrence of both. We compared baseline data in 970 patients (2,2%) with PHr, 2325 patients (5,3%) with local PH, and 39761 patients (91,4%) without PH or PHr. Independent risk factors were obtained by multivariate logistic regression. Increasing age and blood pressure were the only strong risk factors for PHr. High stroke severity, atrial fibrillation, CT hyperdense cerebral artery sign, *i.e.* factors indicating large artery occlusion, were associated with local PH. Functional independence at 3 months was more common in PHr than PH (34% vs 24%, $p < 0,001$), 3 month mortality was lower (34% vs 39%, $p < 0,001$). PH and PHr were equally often symptomatic. The better outcome in PHr is explained by PHr occurring in patients with milder strokes. We concluded that the differences in risk factors likely indicate an influence of underlying small vessel disease in PHr, and large vessel occlusion in PH.