A Stroke Registry Data on the Use of Intravenous Recombinant Tissue Plasminogen Activator in Stroke of Unknown Time of Onset

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Background: Stroke of unknown time of onset (SUTO) constitutes one fifth of all ischemic stroke admissions, and routine use of intravenous recombinant tissue plasminogen activator (IV rtPA) is recommended only in patients with a symptom onset time of less than 4.5 hours. There are limited data on clinical outcome in patients with SUTO versus patients with symptoms onset less than 4.5 hours from onset time. We hypothesized that efficacy and safety outcomes of IV rtPA therapy in selected SUTO patients are comparable to those with known onset time. *Methods:* We compared 90 days' modified Rankin Scale (mRS), rates of symptomatic intracerebral hemorrhage (sICH), in-hospital mortality, and death due to sICH between 3 groups treated with IV rtPA: SUTO, 3 hours or less, and 3.0-4.5 hours from prospective patient admissions between April 1, 2012, and July 31, 2013. *Results:* There were 65 participants in the SUTO group, 186 in the 3 hours or less group, and 51 in the 3.0-4.5 hours group. In-hospital mortality rates were 14.5%, 13.5%, and 11.8%, respectively. sICH risks were 1.5%, 1.6%, and 5.8%, and death rates due to sICH were 0%, 1.1%, and 1.9%, respectively. Ninety days' odds of excellent clinical outcome (mRS score 0-1) were not different between the SUTO group (odds ratio [OR] 1.14, 95% confidence interval [CI]: .63-2.10), the 3 hours or less group (OR .87, 95% CI: .48-1.60), and the 3.0-4.5 hours group (OR .79, 95% CI: .48-1.60) (P = .82). *Conclusion:* Thrombolytic therapy outcome in SUTO is not different from in-license use in our patient population. There is an urgent need to include this patient group in ongoing randomized multicenter trials. **Key Words:** Acute ischemic stroke—recombinant tissue plasminogen activator—stroke of unknown time of onset—in-license treatment.

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Background

Stroke of unknown time of onset (SUTO) constitutes more than one fifth of all ischemic stroke admissions[1-3] and the reported incidence of a subgroup that woke up with their symptoms is 8%-28%.[3-10] Routine use of recombinant tissue plasminogen activator (rtPA) is only recommended in patients admitted less than 4.5 hours from ictus.[11] However, there is increasing stroke register data on favorable safety and clinical outcome following thrombolytic therapy in patients with unknown onset time.[8-10] Despite the significant proportion of SUTO patients within the ischemic stroke population, they are currently excluded from routine treatment with rtPA, due to insufficient clinical outcome data on the efficacy and safety of the use of rtPA, and concerns around theoretical risks of intracranial bleeding and mortality following thrombolytic therapy beyond the current 4.5-hour window. We hypothesized that efficacy and safety outcome of the use of intravenous recombinant tissue plasminogen activator (IV rtPA) in SUTO is comparable to patients treated in-license (<3 hours and 3.0-4.5 hours from symptom onset), when using multimodal computed tomography (CT) to define salvageable penumbra. The hypothesis was based on the assumption that the speed of development of collaterals and the efficacy of a salvageable penumbra vary in different patients, because of the variability of collateral circulations and other yet undefined factors.[12,13]

Materials and Methods

Patient Selection

This is a 3-site, acute stroke unit, case–control study, with informed consent prospectively obtained for off-license treatment, using multimodal CT if clinical symptoms were suggestive of acute stroke. Clinical assessment is by face-to-face between 09:00 and 17:00 hours and via telemedicine between 17:00 and 09:00 hours.

Patients included in this analysis were selected from our Stroke Register Database Research between April 2012 and July 2013. The criteria for inclusion into the stroke register were peer reviewed and agreed upon by a research ethics committee before ethical approval. Data that were prospectively captured include demographic details, baseline National Institutes of Health Stroke Scale (NIHSS) score, neurovascular risk factors, neuroimaging details, premorbid Barthel Index, and treatment for cerebrovascular disease. Data extracted were verified weekly through a peer-reviewed process involving a 2-man adjudicating panel who had access to medical records and electronic patient details but were blinded to the neuroimages, and the following predefined entry criteria were agreed upon for the purpose of group characteristics:

1. Subject selection into the SUTO group treated with rtPA: onset (wake-up stroke inclusive) time, but were last seen normal for more than 4.5 hours, but less than 24 hours before hospital admission. Stroke severity was indicated by an NIHSS score of 4 or higher, if visual quantification of the cerebral blood flow (CBF) : cerebral blood volume (CBV) map demonstrated a mismatch. Those excluded in this group had established single or multiple infarcts on noncontrast computed tomography (NCCT) and matched defect was confirmed on CBF : CBV maps.
2. In the in-license group, the subjects included had a symptom onset of less than 4.5 hours and an absence of intracerebral hemorrhage on NCCT. Excluded were subjects with an Alberta Stroke Program Early CT Score (ASPECTS) of less than 7, single or multiple established recent infarcts on NCCT despite a history of symptom onset less than 4.5 hours.

Clinical Assessment

Routine department management of stroke includes baseline and 24-hour NIHSS scores, Oxford Community Stroke Project clinical stroke classification, NCCT, or multimodal CT. The dose of rtPA given was .9 mg/kg body weight. The modified Rankin Scale (mRS) score was determined at 3 months and then ranked as 0-1 (excellent), 0-2 (favorable), and ≥3 (unfavorable). Other outcome variables examined were mean 24-hour reduction in NIHSS score, in-hospital mortality, 90-day mortality, and symptomatic intracerebral hemorrhage (sICH) rate as defined by Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria.[14]

Imaging Protocol

In this consultant-led therapy model, initial neuroimaging assessments were by NCCT for the in-license group and by multimodal CT for the SUTO group. A Siemens, Somatom, Definition flash, 128-slice multidetector CT scanner (Siemens Medical Solution, Malvern, PA) was used. ASPECTS scoring was carried out on all NCCTs, and patients with a score of 7 or higher in the in-license group were treated with rtPA. In the SUTO group, ASPECTS scoring on NCCT was followed by visual assessment after postcontrast processing for areas of corresponding paucity of blood flow on CT angiography intracranial source images. The following imaging criteria were considered in the definition of mismatch on computerised tomographic perfusion scan (CTP) before thrombolytic therapy:

1. Percentage volume mismatch calculated from the CBF and CBV maps $(\text{CBF} - \text{CBV}/\text{CBV}) \times 100\%$, greater than 20%.[15,16]
2. Infarct core on CBV maps not exceeding one third of ipsilateral middle cerebral artery territory.[17]

Eligible patients were treated with IV rtPA (.9-mg/kg body weight). All patients were managed on an acute stroke, high dependency unit, and subsequently went on to have a 24-hour follow-up NCCT to rule any intracerebral