

Acute management and research of stroke in Taiwan: an update

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Abstract: The presentation discussed certain issues in the management and research of cerebrovascular diseases in Taiwan. In the first part of the presentation, the acute management of stroke in Taiwan, I have revealed the results of the Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) study (rt-PA). TTT-AIS was a multicentre, observational study, which enrolled 244 eligible patients with acute ischemic stroke from 23 hospitals from December 2004 to July 2008. The standard-dose group (0.9 mg/kg) had higher rates of symptomatic ICH and mortality within three months, twice that of the lower-dose group. This pattern was more prominent in older patients. Besides, significantly lower independence rate was also observed among patients ≥ 70 years old receiving standard-dose than lower-dose. This study suggests that the standard dose of alteplase 0.9 mg/kg may not be optimal for treating aged Chinese. However, the optimal dose of rt-PA for ischemic stroke in Chinese should be based on more broad and convincing evidences. Randomized trials of lower versus higher dose of rt-PA are needed. The second part of the presentation discussed about the relationship between age-related cerebral white matter lesions (leukoaraiosis) and jugular venous reflux (JVR), one of the plenty researches about cerebral venous insufficiency in Taiwan. The presentation introduced current evidences and rationales favoring venous ischemia as a role in the pathophysiology of leukoaraiosis.

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Key words : rtPA, ischemic stroke, stroke treatment, jugular venous reflux, leukoaraiosis

Therapy for Acute Ischemic Stroke Study (TTT-AIS)¹⁾

Recombinant tissue plasminogen activator (rtPA) is still the only effective treatment for acute ischemia stroke, which can improve functional outcome. The most tragic side effect of rtPA is intracranial hemorrhage (ICH). It is a hot debate that different optimal doses of anticoagulant and thrombolytics should be applied for Caucasians and Asians. It's also the case in rtPA for ischemic stroke. For coronary disease, the dose to reach an effective coronary patency is 1.25 mg/kg for Caucasian, and lower dose, 0.5 to 0.75 mg/kg for Asian. For ischemic stroke, we wonder if the standard dose of rtPA in American and Europe also is appropriate for Asian people. Japan Alteplase Clinical Trial (J-Act), which used rtPA 0.6 mg/kg for acute ischemic stroke, gives us some clues. The results showed that the safety and efficacy were comparable to that in NINDS study.

In Taiwan, rtPA for ischemic stroke was approved in 2003. For further surveillance, Taiwan Stroke Society launched a multicentre, observational study, the Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) study from December 2004 to July 2008. This study was an internet-

based thrombolysis therapy registration (designs similar to SITS-MOST study). The primary outcome, the safety measures, was the occurrence of symptomatic ICH. The secondary outcome was the efficacy, which used Barthel Index and Modified Rankin Scale (mRS).

241 patients were enrolled in the study. We referred a unit dose of 0.85 to 0.95 to the standard-dose group (n = 116) and <0.85 mg/kg to the lower-dose group (n = 125). All clinical characteristics were similar between these two groups. The rates of SICH were slightly higher in SITS-MOST, NINDS, and J-ACT studies. The mortality within 3 months in this study was less than that in SITS-MOST and NINDS. The good functional outcomes at 3 months were comparable with the results of the SITS-MOST, NINDS, and J-ACT studies. Multiple regression analysis showed that age > 70 years, standard dose of rtPA, and clopidogrel/ticlopidine use were the independent predictors for SICH (NINDS definition) after adjustment for other factors. Patients with standard dose had twice the chance of SICH on NINDS, ECASS, and SITS-MOST definitions, and the lower-dose group had fewer symptomatic ICHs (SICH) and deaths within 3 months and more functional independence though not statistical significant. The outcome differences were strengthened after con-

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sidering the age and dose interaction. Patients aged > 70 years who received both doses had similar baseline variables and clinical demographics. In patients older than 70 years, a significant lower rate of SICH per ECASS and mortality within 3 months, and a significant higher rate of independence (mRS 0-2) in lower-dose group.

Therefore, we conclude that Alteplase 0.9 mg/kg for ischemic stroke seems not optimal for treating aged patients in Taiwan. To determine the appropriate dose in Taiwan people, we are currently organizing a randomized trial of lower versus higher doses.

Jugular venous reflux (JVR) and leukoaraiosis²⁾

The mechanism that cerebral venous disease cause brain tissue ischemia is via cerebral venous hypertension. Increased cerebral venular pressure decreases cerebral perfusion pressure and consequent decreased cerebral blood flow to brain tissue. Besides ischemia, cerebral venous hypertension would cause microvessels (mainly venules) wall hyaline thickened, and brain-blood barrier (BBB) damage which would lead to vasogenic edema and microbleeding.

JVR is defined as venous reflux detected in internal jugular vein (IJV) at rest or during Valsalva maneuver (VM), which is resulted from abnormally reversed venous pressure gradient beyond the competence of IJV vales. Arteriovenous fistula (AVF) in sigmoid sinus which has venous reflux via sigmoid sinus into cerebral venous system mimics the venous reflux in JVR. Several case reports have shown that AVF in sigmoid sinus could cause progressive dementia and symmetric, diffuse white matter lesions. These lesions could be reversed after embolization of the AVF, and SPECT has shown cerebral hypoperfusion within these white matter lesions. Therefore, we hypothesized that JVR might play a role in leukoaraiosis, e.g. age-related white matter changes.

Our recent large-population study showed that the preva-

lence of JVR increases with aging³⁾. Our previous physiological studies⁴⁾ have also shown that VM-induced JVR could cause dilated retinal venular, and influence cerebral blood flow during VM. These results provide evidences that JVR could influence cerebral venous drainage and cerebral blood flow, and might cause cerebral white matter chronic ischemia. The other supporting facts include (1) wider retinal venules are associated with the progression of leukoaraiosis;⁵⁾ (2) dilated intraparenchymal venules radiating out from the posterior horn of ventricles are related to white matter hyperintensities;⁶⁾ and (3) periventricular venule collagenosis, one pathology feature, correlates with leukoaraiosis severity⁷⁾.

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