SVN Stroke and Vascular Neurology

New era of stroke therapy and new challenges

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To cite: Miao Z. New era of stroke therapy and new challenges. *Stroke and Vascular Neurology* 2016;**1**: e000010. doi:10.1136/svn-2016-000010

Received 21 January 2016
Accepted 23 January 2016

▸ http://dx.doi.org/10.1136/svn-2015-000004

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The year 2015 was revolutionary for the treatment of acute ischaemic stroke (AIS) because of publication of multiple large randomised controlled clinical trials (RCTs) on the success of mechanical thrombectomy. Campbell *et al* provided a very comprehensive review of this topic in this issue of *Stroke and Vascular Neurology*. Consequently, the European and Chinese AIS guidelines have both given thrombectomy the highest level of recommendation (I,A). While we celebrate this most significant change in 20 years of stroke therapy, we also begin to contemplate what these new treatment modalities will bring.

The first question is, should the current care protocols be changed? Intravenous thrombolysis has been widely practised in China. The number of patients treated has improved significantly in recent times. The door to needle time has been shortened to a level comparable to the international standard at many large stroke centres. However, the rate of giving intravenous tissue-type plasminogen activator (TPA) is still <10% in China and <5% of patients with stroke would arrive at the hospital within 3 h. Therefore, if we do not make significant changes to the current protocol on acute phase triaging, not many patients with AIS may benefit from these state-of-the-art thrombectomies. We especially need to improve two aspects of care processes. One is to improve dissemination of stroke education to the public, hospital administration and governmental agencies so that they can better understand the benefit of thrombectomy. The second is to standardise the training of the providers. In China, providers who can offer thrombectomy include neurologists, neurosurgeons and interventional radiologists. Their training and ways of providing interventional treatment are quite diverse. Many pursue technical and imaging goals while ignoring the importance of preoperative evaluation of patients. The published trials have taught us that preoperative evaluation of patients with stroke for their stroke subtypes, the location of the blockage, the presence of a penumbra with mismatch and the degree of collaterals is crucial and will impact their outcome. If the training of those performing thrombectomy in China is not standardised, it is perceivable that such treatment modality could be abused or misused and, therefore, lose its effectiveness.

The second question is whether the research on intra-arterial (IA) thrombolysis alone should be continued? Before the arrival of mechanical thrombectomy, IA thrombolysis was one of the treatment modalities for patients with AIS. From PROACT II (Prolyse in Acute Cerebral Thromboembolism II)[1] and MELT (Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial Japan),[2] we have learned that IA thrombolysis alone could improve the patient's outcome. In China, a retrospective review also showed that IA urokinase performed better recanalisation of the arteries and improved outcome. However, these trials did not have rigorous preoperative imaging analysis and screening. Therefore, if the same preoperative screening of patients and their vasculature were implemented, such as in the ESCPE and SWIFT PRIME trials for IA thrombolysis alone, would the outcome be as good clinically? Compared to IA thrombectomy, simple IA thrombolysis is technically easier to perform and financially more economical. If urokinase is used, then the fee for the entire procedure is around 10 000 RMB. On the contrary, the use of a Solitaire FR thrombectomy device would incur a fee of around 70 000 RMB.

The third question is, can the results of these well-conducted RCTs be applied to routine daily clinical practice? It is well know that every patient with stroke is different. Many patients with stroke may require multiple interventional therapies to clear the clot (Penumbra, Solitaire or thrombolysis). Individualising the treatment plan for each patient with AIS is the likely procedure in the future. For example, many patients with AIS may have in situ thrombus because of

high-grade arterial stenosis prior to its occlusion, making it technically difficult to perform thrombectomy. In these patients, the catheter cannot be advanced through the point of stenosis—the device cannot reach the area of blockage, it cannot be deployed to catch the thrombus and be safely withdrawn, and the sheer force of the device may cause endothelial damage or rupture of the artery because of plaque hardness. In these patients, perhaps IA thrombolysis would be more appropriate. The published RCTs did not address these issues.

The fourth question is, does the presence of a conflict between the time window of treatment and imaging analysis on the selection of patients with AIS for intervention exist? The current guideline has stated that a patient with AIS would be a good candidate to intervene if their area of infarction is <70 mL, or ASPECT score is >6 (better collaterals). The question is, should patients with AIS who present to the emergency room beyond 12 h but have imaging findings suitable for treatment be treated? Therefore it remains to be determined whether a patient with AIS should be treated based on the time window or on imaging findings.

The fifth question is, should newer thrombolytic agents continue to be studied for AIS? Many new agents such as TNK-TPA[3 4] or desmotaplase[5] have not performed well in clinical trials, or are still being studied for intravenous thrombolysis. Would these agents then be more effective in patients given IA?

The last question is, should intravenous thrombolytics be avoided when IA therapies are being considered? All large published RCTs have pointed out that the combination of intravenous TPA plus IA thrombectomy is superior to intravenous TPA alone. What role did intravenous TPA really play in the combination therapy then? Would new trials be needed to prove that simple IA thrombectomy is as good without intravenous TPA being given first?

As has been reviewed by Campbell *et al*, we have entered into an exciting era of providing effective and safe treatment to patients with AIS. On the contrary, these proven treatment modalities have raised more questions on patient selection, the use of a time window or imaging studies, the role of IA thrombolysis alone or thrombectomy alone and the use of newer thrombolytics for IA treatment. However, it is clear that we have effective and safe options to treat patients with AIS who present early, and imaging studies show viable penumbra and good collaterals. We have more work to carry out in order to elucidate other questions, as mentioned earlier, and perhaps provide more personalised therapy to our patients in the near future.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

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