Mechanical thrombectomy for acute ischemic stroke: the therapeutic window is larger but still “time is brain»

The International Stroke Conference, held in Los Angeles in January 2018 marked a step forward in stroke management, as it saw the presentation of the American Heart Association/American Stroke Association (AHA/ASA) 2018 guidelines for the early management of patients with acute ischemic stroke (Powers et al., 2018). One of the new messages of these guidelines, compared with the 2015 ones (Powers et al., 2015), is the strong recommendation to perform mechanical thrombectomy with a stent retriever within six hours of onset of symptoms without prior intravenous (iv) alteplase in stroke patients older than 18 years with non-significant pre-stroke disability (i.e., a modified Rankin scale score, mRS ≤ 1), a documented causative occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA) segment M1, and specific clinical (i.e., National Institutes of Health Stroke Scale score ≥ 6) and radiological (i.e., Alberta stroke program early CT score, ASPECTS ≥ 6) features (Powers et al., 2018). According to the 2018 guidelines, while iv alteplase should be administered to eligible patients even if endovascular treatments are being considered, observation after iv alteplase to assess for clinical response should be avoided in those under consideration for mechanical thrombectomy, because the risk of such observation would overwhelm its benefit (Powers et al., 2018).

Even though it may seem obvious that mechanical removal of the clot is likely to improve clinical outcome more than iv thrombolysis in acute ischemic stroke, mechanical thrombectomy was accepted as the gold standard for patients with ICA or MCA segment M1 occlusion only after the publication of six randomized controlled trials (RCTs), namely MR CLEAN (Berkhemer et al., 2015), SWIFT PRIME (Saver et al., 2015), EXTEND-IA (Campbell et al., 2015), ESCAPE (Goyal et al., 2015), REVASCAT (Jovin et al., 2015), and THRACE (Bracard et al., 2016). A recent meta-analysis of five of these RCTs showed that 46.0% patients randomized to endovascular treatment, plus iv thrombolysis when eligible, reached a good disability outcome (i.e., mRS = 0–2 at 90 days; OR = 2.35) compared to 26.5% of the control group, who underwent iv thrombolysis or no treatment (Goyal et al., 2016). The odds of a better disability outcome at 90 days in the mechanical thrombectomy group declined with longer time from symptom onset to arterial puncture (OR at 3 hours = 2.79, OR at 6 hours = 1.98, OR at 8 hours = 1.57), indicating that each one-hour delay to reperfusion was associated with worse disability (OR = 0.84) and less functional independence (OR = 0.81; Saver et al., 2016). Based on the direct correlation between disability outcomes at 90 days and time from symptom onset to arterial puncture, any cause of delay to mechanical thrombectomy, including observing for a clinical response after iv alteplase, should be avoided (Powers et al., 2018).

Older RCTs documented endovascular therapy not to be superior to standard treatment with iv thrombolysis (Ciccone et al., 2013). The reasons for better outcomes in most recent RCTs on mechanical thrombectomy include greater attention to the need for shorter time to imaging and treatment, more accurate imaging to document large vessel occlusion, and technological improvements resulting in second generation stenting devices, which may achieve complete or near-complete recanalization in 70-85% of patients in comparison to 40-50% for first generation ones.

Two very recent RCTs suggest that the time window for mechanical thrombectomy may be further expanded in selected sub-populations of patients, to up to 16 hours according to the DEFUSE3 trial (Albers et al., 2018a), and to up to 24 hours according to the DAWN trial (Nogueira et al., 2018). Surprisingly, the outcomes of these two RCTs seem to be even better than those of previous ones that adopted shorter intervention windows, suggesting the presence of a late window paradox, which is explained by the more accurate selection of patients thanks to newer imaging techniques (i.e., perfusion CT, diffusion-weighted MRI), which serve to identify the so-called slow-growing infarcts (Albers et al., 2018b).

After the introduction of iv thrombolysis for the treatment of acute stroke in the 1990s (Haley et al., 1992), and the definition of the three-hour time window, the motto “time is brain” was created to underscore the importance of speeding up all the phases of acute stroke management, from pre-hospital assessment and transportation, to emergency evaluation and stroke unit admission (Gomez et al., 1993). On the basis of the typical final volume of a large vessel, supratentorial ischemic stroke (average = 54 ml, range = 19-100), the duration of non-lacunar stroke evolution (average = 10 hours, range = 6-18), and the number of neurons in the human forebrain (average = 22 billion), a typical large vessel acute ischemic stroke is estimated to cause the loss of 1.9 million neurons, 14 billion

synapses, and 12 km of myelinated fibers per minute (Saver, 2006). Compared with the normal rate of neuron loss in brain aging, the ischemic brain ages 3.6 years each hour without treatment (Saver, 2006). A large and exciting bulk of evidence on the treatment of acute ischemic stroke with iv thrombolysis and mechanical thrombectomy has accumulated in the last two decades, and probably the best is yet to come. However, all those dealing with acute stroke patients should keep in mind that, despite the progressive widening of the therapeutic window, still "time is brain".

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