

## **CAN ULTRASOUND ENHANCE THE RECANALIZATION EFFECT OF tPA?: YES**

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Stroke is the first cause of disability worldwide. Intravenous thrombolysis with alteplase has changed the acute stroke treatment paradigm in the 21st century. It is still the first treatment with proven efficacy that we should give in most instances, whenever possible, in the first 4.5h after symptoms onset<sup>1</sup>.

However, even in these treated patients the results are not satisfactory. In an international registry (SITS) including patients treated with alteplase in daily routine, 46% of patients still have disability at 3 months, being dependent on others, or are even dead<sup>2</sup>.

The main reason for this lack of efficacy is the modest recanalization rate of the occluded artery with intravenous thrombolysis, being about 25-40%<sup>3</sup>. On the other hand, it is well-known that the speed of recanalization is crucial for the success of clinical recovering<sup>4</sup>.

Searching for alternative treatments, thrombolytic drugs have been administered locally, although there is not a good evidence of a greater efficacy of intra-arterial tPA<sup>5</sup>. More recently, mechanical thrombectomy has been shown to be safe and significantly improve ischemic stroke patients' outcome, when treated in the first 6 hours from symptoms onset<sup>6</sup>. Nevertheless, this endovascular treatment requires a highly specialized organization and very well-trained neuro-interventionists, only available in some centers.

On the other hand, most stroke units have access to transcranial Doppler (TCD) devices, and vascular neurologists are often familiarized with this simple, harmless, bedside technique. TCD assists in localizing the occlusion site, evaluating the cerebral hemodynamics, identifying patients with high risk for no recanalization with iv-tPA, monitoring the effect of this drug, and can even assist in enhancing the recanalization effect of tPA.

Sonothrombolysis, the use of ultrasound to help dissolve the clot at arterial occlusion, is an innovative reperfusion therapy in acute ischemic stroke. The finding that monitoring patients with TCD during the administration of intravenous tPA increased the rate of recanalization<sup>7</sup> launched multiple clinical trials.

Augmentation of recanalization can be achieved safely combining tPA with diagnostic transcranial Doppler, which delivers mechanical pressure waves to the thrombus, exposing more its surface and thus increasing the penetration of circulating tPA into the thrombus.

In the CLOTBUST trial<sup>8</sup>, 83% of patients achieved any recanalization (46% complete, 27% partial) with tPA+TCD vs 50% (17% complete, 33% partial) with tPA alone within 2 hours of treatment (P=0.001). Sustained, complete recanalization at 2 hours was 38% vs 13%, respectively (P=0.03).

The treatment of acute ischemic stroke can be further improved by ultrasound and microbubbles in combination with thrombolytic drugs. Molina<sup>9</sup> has shown that administration of microbubbles induces further acceleration of US-enhanced thrombolysis in acute stroke, leading to a more complete recanalization and to a trend toward better short- and long-term outcome. Most excitingly, ultrasound and microbubbles may be effective in clot lysis of ischemic stroke even without additional thrombolytic drugs<sup>10</sup>.

A meta-analysis<sup>11</sup> of 6 randomized and 3 nonrandomized clinical studies of sonothrombolysis showed that any diagnostic ultrasound monitoring can at least double the chance of early complete arterial recanalization at no increase in the risk of symptomatic intracerebral hemorrhage.

Also a recent Cochrane review<sup>12</sup> of all the randomized studies published on ST reported significantly more recanalization and better clinical outcome, with no effect on mortality, when ST was added to alteplase in acute ischemic stroke treatment.

An interesting recent study<sup>13</sup> compared the efficacy of different acute reperfusion therapies for acute ischemic stroke, in a comprehensive benefit-risk analysis of 13 randomized and 5 nonrandomized clinical trials. It concluded that intravenous thrombolysis with tenecteplase and sonothrombolysis had the higher benefit-to-risk ratio among investigational reperfusion therapies. The authors postulate that the combination of sonothrombolysis with IV administration of tenecteplase could be a potentially promising therapeutic option deserving further investigation.

There are currently other ongoing studies. ULTRAS study aims to further define the efficacy of ST in acute ischemic stroke, where patients will be randomized to receive either tPA alone or tPA + US. Sonothrombolysis for acute ischemic stroke is also being tested in a pivotal efficacy

multinational trial called CLOTBUSTER<sup>14</sup>, where an operator-independent device, which can be quickly mounted by medical personnel with no prior experience in ultrasound, has a multi-transducer assembly to cover conventional windows used for transcranial Doppler examinations.

Towards to the future, plasmin-loaded echogenic liposomes with ultrasound-mediated release at thrombus site have shown promising results<sup>15</sup> and might be useful in stroke treatment. On the other hand, regarding the influence of ultrasound frequency on ultrasound transmittance through the human skull, and for safer and more efficient sonothrombolysis therapies, accurate estimation of ultrasound transmittance through the human skull is being studied, using modulated waves, which might in the future allow individual adaptation<sup>16</sup>.

In conclusion:

- Randomized clinical trials have shown sonothrombolysis to be safe and effective in a faster recanalization of the occluded vessel in acute ischemic stroke.
- A meta-analysis of 6 randomized and 3 nonrandomized clinical studies of sonothrombolysis clarified that any diagnostic ultrasound monitoring can at least double the chance of early complete arterial recanalization at no increase in the risk of symptomatic intracerebral hemorrhage.
- A recent Cochrane review of all the randomized studies published on sonothrombolysis reported significantly more recanalization and better clinical outcome, with no effect on mortality, when sonothrombolysis was added to alteplase in acute ischemic stroke treatment.
- Investigation is ongoing with larger clinical trials to establish the most effective and safe way to apply sonothrombolysis in the routine management of the acute ischemic stroke patient.
- Future possibilities include specific targeting of thrombus with local drug delivery with US-sensitive liposomes.

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