Letters to the Editor

Significance of Experimental Infarct Size as an Indicator of Therapeutic Efficacy in Humans

To the Editor:

We would like to make a comment not in particular to the article by Shimamura et al but to the use of infarct size in animal experiments as a guide to human cerebrovascular research. Many human studies of treatments with neuroprotective agents for acute ischemic stroke, which had good experimental potential, had disappointing clinical results. This failure can be attributed to many factors. One of the main problems is that reliance on infarct size measurement alone in animals can be misleading as an indicator of therapeutic efficacy in humans.

Moreover, some compounds (e.g., basic fibroblast growth factor, osteogenic protein-1) have been associated with functional improvement without affecting infarct size in animals.

It is also obvious that histological end points cannot tell whether surviving neurons are functional or dysfunctional or will go on to die in a delayed fashion, and they are less predictive of long-term histology than early behavioral assessments.

We would like to add an alternative hypothesis in the problem of experimental infarct size and its clinical implications. Many studies are based on the supposition that proinflammatory agents are detrimental for the brain and that their elevated appearance after ischemia must be somehow diminished. The offered proof is the increased infarct size, which they usually produce in experimental animals. On the other hand, we can suppose that these agents just help confine and finally clear the damaged brain area. In such a case, the infarct size would be increased, but the chances for the rest of the brain would be conceivably better. Increased intracranial pressure could make the problem more complex, but the main idea remains: it is easier to suppose that what the human body does should be supported rather than to think that it should be reversed.

Let us take the example of tumor necrosis factor-α (TNF-α). Its action in ischemia is described as both detrimental and neuroprotective, depending on the experimental conditions. Elevated serum level of TNF-α is observed after severe head injury and trauma. TNF-α mRNA is elevated, especially in the first 5 days. Intraventricular injection of TNF-α one day before middle cerebral arterial occlusion exacerbates tissue injury and is reversed by anti–TNF-α. On the other hand, transgenic animals lacking TNF-α receptors develop significantly larger damage to neurons after focal cerebral ischemia or epileptic seizures. TNF-α pretreatment of cultured endothelial cells, astrocytes or neurons protects them to the same degree as hypoxic preconditioning. Importantly, if necrosis is attenuated by therapy (i.e., by reperfusion or antiexcitotoxic agents), then apoptosis may be unmasked or even promoted.

These experimental data can be considered consistent under our hypothesis. Therefore, assessment of therapeutic efficacy in preclinical studies should require, in addition to infarct size, demonstration of benefit on functional measures of motor, sensory, or cognitive deficits.

Our conclusion is that experimental infarct size cannot serve by itself as a prognostic indicator in human studies, especially when pro- or antiinflammatory agents are tried.

Disclosures

None.

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