Recanalization Rates Can Be Misleading

To the Editor:

We read with interest Rha and Saver’s review of relationships between recanalization and outcome and commend them on their comprehensive review of pertinent literature. However, we disagree with their main conclusion that recanalization may substitute for measurement of clinical outcome.

The central finding that leads Rha and Saver to their conclusion is that those patients who recanlized fared better than those that did not. We contend that this conclusion is valid only if a fixed dose of agent was used and the groups were comparable at baseline. In nearly every cohort there will be individuals that do not respond to a specific therapy regardless of dose and so are subject primarily to the toxicity of the intervention as dose is raised to reach a specific clinical goal (in this case, recanalization). Their logic is valid only if there is no added risk associated with additional efforts to pursue recanalization.

To properly relate dose to outcome requires a fixed or random dose design such that results are not skewed by differences in exposure. In simplest terms, if a subset of acute ischemic stroke patients had resistant clots and were subjected to either additional time, mechanical manipulation or doses of thrombolytic agent, then it is conceivable that they experienced additional toxicity. It is also possible that more resistant clots are themselves a marker for different pathogenesis or severity of the ischemic insult to the vasculature. Although still not ideal, this comparison is more valid for intravascular trials when treatment is not usually linked to recanalization, but will not be valid for interventional trials where recanalization is the goal. Although limits are often placed on the intervention (eg, a ceiling dose of thrombolytic or number of passes for mechanical thrombectomy), these limits are not scientifically based and agents are often used in multiple combinations.

There may be particular subgroups in which recanalization may have paradoxical results. For example, in hyperglycemic stroke patients, early recanalization was associated with worse outcomes, and in our retrospective analysis of the CLOTBUST trial, better outcomes at 3 months was related to exposure to ultrasound, not to enhanced recanalization rates. As discussed by Rha and Saver, we have also proposed that the key to better outcomes is extent of tissue perfusion, rather than simply proximal recanalization.

In the coronary arteries in the setting of an acute MI, aggressive measures undertaken to increase recanalization rates have not translated into better outcomes. Although the reason for this “paradox” has not been established, there is increased time, mechanical manipulation and/or agents involved in achieving higher or more rapid recanalization rates.

Consistent with this coronary literature, our review of intra-arterial therapies for stroke indicated that the best performers used lower doses of thrombolytic and included the only series with fixed dose agent not linked to recanalization success.

An additional problem with surrogate use of recanalization rates is that it does not establish whether the treatment of interest itself is better than either no or alternative treatments. Simply because those that recanalized did better than those that did not does not mean that overall the patients did better than if they had received no therapy.

In the absence of sufficient number of interventional “fixed-dose” trials, and without a gold standard by which to compare overall outcomes of an intervention, we believe Rha and Saver’s contention is premature, at least when it comes to interventional therapy. Worse yet is if these suggestions are translated into clinical practice to “force” recanalization, even if within limits. We propose that our efforts would be better spent on first establishing the clinical efficacy of these methods and improving our understanding of factors that contribute to recanalization, enhancing tissue perfusion and minimizing adverse consequences.

Disclosures

None.

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Stroke. 2007;38:e103; originally published online September 6, 2007;
doi: 10.1161/STROKEAHA.107.492405
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/38/10/e103

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