Occlusion of the M2: confusion about reperfusion

R. Loch Macdonald, M.D., Ph.D.
Division of Neurosurgery, St. Michael’s Hospital, Labatt Family Centre of Excellence in Brain Injury and Trauma Research, Keenan Research Centre of the Li Ka Shing Knowledge Institute of St. Michael’s Hospital, Department of Surgery, University of Toronto, Ontario, Canada

In this issue of the Journal of Neurosurgery, Rahme and colleagues report an interesting subgroup analysis of patients from the recombinant Prolyse in Acute Cerebral Thromboembolism (PROACT) II, Interventional Management of Stroke (IMS), and IMS II studies. They studied patients with solitary occlusions of the M2 segment of the middle cerebral artery. The 63 patients were divided into those in whom successful reperfusion was achieved after 2 hours (31 patients, 49%) and those without successful reperfusion (32 patients). The 2-hour time is not from the time of onset of symptoms. There were no statistically significant differences in intracerebral hemorrhage or mortality between patients with or without reperfusion, although there were more symptomatic hemorrhages in the reperfused group (5 vs 0 patients). This would be expected to worsen outcome in the reperfused group. Also, the reperfused group demonstrated a trend toward higher baseline plasma glucose concentration, which also is a negative prognostic factor for outcome in ischemic stroke. Despite this, outcome was not significantly different between the groups, with 58% of reperfused and 53% of nonreperfused patients achieving functional independence at 3 months.

This paper builds on earlier studies addressing the same issue, including the authors’ prior paper on the subgroup of patients with M2 occlusions in PROACT II. The PROACT II study compared patients treated with heparin for ischemic stroke who were randomized to this standard care or to additional intraarterial (IA) thrombolysis with prourokinase. Overall, there was better outcome with IA prourokinase as well as increased odds of reperfusion. Also, in the subgroup with M2 occlusions, IA therapy increased the odds of reperfusion and there was a trend toward improved outcome. My question is that in that study, the controls were not treated with intravenous (IV) thrombolytics. The authors of the current paper comment that patients in PROACT II had IA recombinant tissue plasminogen activator (r-tPA), but I think it was prourokinase. But more importantly, they note that the aforementioned benefit was not observed in the IMS studies and suggest that this is because of more hemorrhages in the r-tPA–treated patients in the IMS. That is possible, but isn’t it also possible that it is because IV r-tPA, which was given in the IMS studies, also improves outcome?

The present analysis shows that although the concept that “time is brain” is true (i.e., the longer the brain is ischemic, the greater the damage), it is more complicated than that. Simplistically, it seems likely that the faster reperfusion is achieved, the better. However, demonstrating this in a clinical trial will be influenced by the interactions of time (the longer to reperfusion the worse the outcome), size and location of infarction, collateral circulation that influences the proportions of ischemic penumbra versus core, clinical deficit, and risks associated with interventional treatment and reperfusion. This article is based on the idea that in ischemic stroke, the smaller and more distal the cerebral artery that is blocked, the smaller and less disabling the stroke will be, so the benefit of a risky interventional procedure will be lower. Of course the artery size rule doesn’t apply to small perforating arteries supplying critical brain structures, but for the 3 major cerebral arteries there should be some truth to it. Thus, at some point, the risks associated with thrombolysis, reperfusion, and endovascular procedures will outweigh the benefit.

For M2 occlusion, this analysis suggests that the benefit of endovascular methods in achieving recanalization is small or nonexistent. The caveats are mentioned, which are mainly that thrombolytic drugs were used to achieve reperfusion, rather than mechanical methods, which may have a lower risk of causing hemorrhage and a lower likelihood of achieving reperfusion. Also, the time to reperfusion is variable and it remains an open question whether faster reperfusion would be beneficial. This is a post hoc analysis of subgroups of 1 randomized and 2 nonrandomized studies. It is always necessary to consider the limitations of subgroup analyses, although I don’t think most of them apply here.

One point is that the patients in the IMS studies were treated with r-tPA, so it is not known whether the endovascular treatment of patients with M2 occlusions who are not eligible for r-tPA would be effective.
This paper is particularly of interest given the findings of the IMS III and SYNTHESIS Expansion studies. In IMS III, 656 patients were randomized to intravenous r-tPA within 3 hours of stroke versus additional endovascular therapy. The study was stopped early and reported that there was no difference in outcome at 90 days based on the modified Rankin Scale score. Reperfusion was more likely after endovascular therapy, but this was not associated with improved clinical outcome. The SYNTHESIS Expansion trial was similar, except inclusion was within 4.5 hours of stroke. It also found no difference in outcome between the groups. As expected, numerous questions about and explanations for these negative results have been published. A key point is that many of the patients in these studies did not have large-artery occlusions or had distal artery clots, which would fit with the current analysis suggesting less benefit of reperfusion in such cases.

A concept brought out by this analysis is that of the pragmatic versus explanatory clinical trial. Schwartz and Lellouch defined pragmatic trials as ones that apply the tested treatments under the conditions in which they are applied in clinical practice. An explanatory trial is designed to answer a more specific mechanistic hypothesis. The SYNTHESIS Expansion study was a pragmatic trial. Given the studies showing no benefit to endovascular therapy, one might ask whether mechanical methods of reperfusion were not being explanatory; in other words, the measurement methods become obsolete or a variable is not considered because data are not available about it. New endovascular therapy trials are, for example, focusing on patients with known occlusions and the elusive role of perfusion-diffusion mismatch.

In summary, this analysis adds to a growing body of literature suggesting that patients with M1 occlusions have better outcomes than those with more proximal occlusions, and thus that efforts to achieve reperfusion are less likely to show benefit. Some remaining questions are the extent to which this applies to patients who are not eligible for r-tPA, as well as whether mechanical methods of reperfusion and/or faster reperfusion are more effective.

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References


Response

RALPH RAHME, M.D.,1,2 SHARON D. YEATTS, PH.D.,3 TODD A. ABRUZZO, M.D.,4 LINCOLN JIMENEZ, M.D.,4 LIQIONG FAN, M.D.,4 THOMAS A. TOMISKE, M.D.,4 ANDREW J. RINGER, M.D.,4 ANTHONY J. FURLAN, M.D.,4 JOSEPH P. BRODERICK, M.D.,4 and POOJA KHATRI, M.D., M.SC.6

Departments of 1Neurology, 2Radiology, and 3Neurology, University of Cincinnati, Ohio; 4Department of Neurosurgery, University of Louisville, Kentucky; 5Department of Medicine, Medical University of South Carolina, Charleston, South Carolina; and 6Department of Neurology, Case Western Reserve University, Cleveland, Ohio

We would like to thank Dr. Macdonald for this very thorough and insightful editorial. We believe that the main finding of our study is that patients with an acute M1 occlusion have significantly better outcomes than those with more proximal occlusions, with a more than 50% chance of functional independence at 3 months, even when successful angiographic reperfusion is not achieved at 2 hours. In contrast, whether early reperfusion can further improve outcome in these patients has yet to be determined. We have observed a 5% outcome benefit favoring the reperfused group. Although potentially clinically significant, this difference did not reach statistical significance. Yet, the study was underpowered and the reperfused group had higher baseline serum glucose levels, a well-established negative prognosticator in ischemic stroke.