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.⁴⁻⁶⁻¹⁰ 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.⁵ 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.⁵ 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.⁴ 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.⁷ 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.1,2 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.3 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.11,12 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 stroke treatment, more explanatory trials are being proposed. One difficulty is that knowledge advances and pragmatic components of studies can be criticized for 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 M2 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. (http://thejns.org/doi/abs/10.3171/2013.12.JNS132245)

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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.,1 LIQIONG FAN, M.D.,2 THOMAS A. TOMISCK, M.D.,4 ANDREW J. RINGER, M.D.,4 ANTHONY J. FURLAN, M.D.,5 JOSEPH P. BRODERICK, M.D.,6 AND POOJA KHATRI, M.D., M.SC.6

Departments of Neurosurgery, Radiology, and Neurology, University of Cincinnati, Ohio; Department of Neurosurgery, University of Louisville, Kentucky; Department of Medicine, Medical University of South Carolina, Charleston, South Carolina; and Department 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 M2 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.6
Moreover, there was a trend toward more symptomatic hemorrhages in the reperfused group, and it could be that some of these would have been avoided by the use of mechanical rather than pharmacological revascularization techniques. Finally, the study cohort was very heterogeneous, particularly in terms of treatments received. For instance, as Dr. Macdonald points out, it is possible that, in addition to an earlier time to treatment, routine administration of IV r-tPA in the IMS studies\textsuperscript{4,5} may have led to overall better clinical outcomes than those in PROACT II,\textsuperscript{3} in which only IA therapy and low-dose IV heparin were offered to the treatment group. Likewise, a correlation between angiographic reperfusion and clinical outcome in IMS may have been blurred by the beneficial effects of IV r-tPA. Given these multiple confounding variables, it remains nearly impossible to draw firm conclusions regarding early reperfusion and outcome in patients with M\textsubscript{2} occlusions.

We do agree with Dr. Macdonald that the relation between time to reperfusion and clinical outcome is quite complex and can be affected by many factors, including the patient’s baseline neurological condition, time of presentation, and quality of leptomeningeal collateral vessels. The quality of collateral vessels in particular has recently been shown to correlate strongly with the success of reperfusion and clinical outcome.\textsuperscript{7} This may be particularly true for solitary M\textsubscript{2} occlusions, for which multiple potential sources of collateral flow exist, including the anterior cerebral artery, posterior cerebral artery, and the other M\textsubscript{1} branch or branches. We have previously shown that, compared with heparin alone, IA thrombolysis is effective in achieving angiographic reperfusion of acute M\textsubscript{2} occlusions and is likely to improve patient outcome.\textsuperscript{8} However, whether IA therapy is superior to IV thrombolysis in these patients remains to be seen. Recent data suggest that this might be the case,\textsuperscript{9} although this has yet to be demonstrated in a randomized controlled clinical trial. In a post hoc subgroup analysis of patients with confirmed large-vessel occlusions (including M\textsubscript{2}) enrolled in IMS III, IA-IV therapy was associated with significantly higher rates of early reperfusion and functional independence at 90 days compared with IV thrombolysis alone (modified Rankin Scale Score 0–2: 47.2% vs 38.5%, \(p = 0.01\)) (Demchuk AM; IMS III: Comparison of outcomes between IV and IV/IA treatment in baseline CTA confirmed ICA, M\textsubscript{1}, M\textsubscript{2}, and basilar occlusions. Paper presented at International Stroke Conference 2013, American Heart Association/American Stroke Association, Honolulu, HI, February 7, 2013). A subgroup analysis of IMS III specifically looking at patients with M\textsubscript{2} occlusions is underway and may provide additional insights into this matter.

In light of the recently published results of the IMS III and SYNTHESIS Expansion trials,\textsuperscript{1,2} there is an impetus for better selection of patients with acute stroke for IA therapy. Those with large-vessel occlusions tend to have larger ischemic territories at risk and are less likely to respond to IV thrombolysis alone. Such patients, as well as those presenting outside the time window for and/or with contraindications to IV thrombolysis, are potential candidates for IA therapy. In general, the more distal the occlusive clot is in the arterial tree, the more likely IV thrombolysis is to be effective and the lower the benefit-risk ratio of IA therapy is. The point where these 2 imaginary lines intersect is probably somewhere along the M\textsubscript{2} segment of the middle cerebral artery, its exact location being highly variable from one patient to another and dependent on multiple factors, including neurological condition, time of presentation, and leptomeningeal collateral vessels. Thus, until more data become available, we propose that selection of patients with an acute M\textsubscript{2} occlusion for IA therapy should be performed on a case-by-case basis.

References

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