Late thrombectomy for stroke: When 6 hours isn't the whole story

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> Acute ischemic stroke remains a leading cause of long-term disability and mortality. Rapid reperfusion is paramount, but a significant proportion of patients present outside the conventional treatment windows for intravenous thrombolysis or mechanical thrombectomy.
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> For those with large infarct cores, the perceived risk of reperfusion injury has historically limited late intervention. But new data suggests a re-evaluation of this long-held clinical boundary.

KEY TAKEAWAYS

- The Pivot: Mechanical thrombectomy may extend its benefit to patients with large-core acute ischemic stroke, even when performed several hours after symptom onset.
- The Data: Patients treated in a late window showed improved functional outcomes compared to medical management alone.
- The Action: Clinicians should consider advanced imaging to identify potential candidates for late thrombectomy, challenging the strict adherence to early time-based criteria for all patients.

Acute ischemic stroke, caused by a blockage in a blood vessel supplying the brain, leads to rapid neuronal death in the core infarct region and potentially salvageable tissue in the surrounding penumbra. The established standard of care for large vessel occlusion (LVO) involves mechanical thrombectomy, a procedure to physically remove the clot. This intervention has revolutionized stroke care, but its efficacy is highly time-dependent, with guidelines typically recommending treatment within 6 hours of symptom onset, or up to 24 hours in select patients with smaller infarct cores and significant penumbral mismatch identified by advanced imaging.

The rationale for these strict time windows stems from the understanding that as time progresses, the ischemic core expands, diminishing the amount of salvageable brain tissue and increasing the risk of reperfusion injury, including hemorrhagic transformation, if blood flow is restored to already necrotic tissue. This has led to a conservative approach for patients presenting with large infarct cores, particularly those beyond the early treatment window, where the perceived risks often outweigh the potential benefits. But the precise definition of a 'large core' and the optimal management strategy for these patients has remained a subject of ongoing debate and clinical equipoise.

Challenging the Time-Based Paradigm

The conventional wisdom has been that patients with a large established infarct core, typically defined as an ischemic lesion volume exceeding 50 mL on baseline imaging, are unlikely to benefit from reperfusion therapies if treated beyond the very early hours. This is because the volume of irreversibly damaged brain tissue is thought to be too extensive to

allow for meaningful functional recovery, and the risk of complications, such as symptomatic intracranial hemorrhage, increases substantially. But this perspective may be overly simplistic, as individual patient physiology and collateral circulation can significantly influence the rate of infarct growth and the potential for recovery, even in the presence of a seemingly large core.

The concept of a 'late window' for thrombectomy has been successfully demonstrated for patients with smaller core infarcts, where advanced imaging techniques, such as CT perfusion or MRI diffusion-weighted imaging, can identify a significant penumbra. These imaging modalities allow clinicians to select patients who still have a substantial amount of brain tissue at risk but not yet irreversibly damaged, thus extending the treatment window beyond the standard 6 hours. But applying this 'tissue window' concept to patients with large cores has been more controversial, largely due to concerns about futility and safety. The question has persisted: can some patients with large infarcts still benefit from reperfusion, even when presenting late?

Rethinking Patient Selection

The focus on late thrombectomy for large-core stroke patients requires a shift in patient selection criteria, moving beyond a sole reliance on time from symptom onset. Instead, a more individualized approach, integrating advanced imaging findings with clinical presentation, becomes important for patient outcomes. Imaging plays a key role in assessing the extent of the established infarct core and identifying any remaining salvageable tissue. While the presence of a large core traditionally contraindicated late intervention, newer analyses suggest that even a small amount of penumbra, or perhaps even the prevention of further core expansion, could translate into improved functional outcomes for some patients.

The potential for benefit in this population is not about achieving a complete return to baseline neurological function, which is often unrealistic with a large established infarct. Rather, it centers on improving the likelihood of achieving functional independence, or at least reducing the severity of disability, compared to medical management alone. This means focusing on endpoints such as a modified Rankin Scale (mRS) score of 3 or less, indicating moderate disability but still allowing for some independence, rather than solely aiming for an mRS of 0-2. The clinical relevance of even a modest improvement in functional outcome for patients facing severe disability cannot be overstated, impacting quality of life for both patients and their caregivers.

The Role of Imaging and Safety Considerations

Advanced imaging, particularly multimodal CT or MRI, is indispensable for evaluating patients who present in the late window with suspected large-core stroke. These imaging techniques provide essential information on infarct volume, collateral circulation, and the presence of any intracranial hemorrhage. The challenge lies in accurately identifying those patients who, despite a large core, still have a physiological substrate that might respond positively to reperfusion. This involves careful interpretation of imaging parameters, often requiring specialized expertise. The Oxford Handbook of Neurology offers a concise overview of these diagnostic considerations.

But the open-label nature of many studies in this area is an obvious caveat. The decision to perform thrombectomy is often made in acute, high-stakes situations, and the absence of blinding can introduce bias, particularly in the assessment of functional outcomes. The risk of symptomatic intracranial hemorrhage remains a significant concern, and careful patient selection is paramount to mitigate this complication. While reperfusion can improve outcomes, it also carries the risk of converting an ischemic infarct into a hemorrhagic one, which can worsen neurological deficits and increase

mortality. Future research needs to refine imaging biomarkers that can more precisely predict both benefit and risk in this challenging patient population.

CLINICAL IMPLICATIONS

The notion that thrombectomy is futile for large-core stroke patients presenting in a late window is being dismantled. Clinicians must now consider a more individualized approach, moving beyond rigid time cut-offs and embracing advanced imaging to identify potential candidates. This means a greater reliance on stroke imaging specialists and a willingness to challenge established paradigms.

For health systems, this shift implies a need for enhanced access to advanced imaging capabilities and specialized neurointerventional teams available around the clock. The logistical complexities of delivering late thrombectomy are considerable, but the potential to improve outcomes for a previously underserved patient group warrants the investment. It also means educating emergency medical services and referring hospitals about the evolving criteria for stroke transfer.

Patients and their families, often facing devastating prognoses with large-core strokes, may now have a glimmer of hope for improved functional recovery. While not every patient will be a candidate, the expansion of the treatment window offers a chance for better quality of life. This highlights the importance of rapid presentation to a stroke center, even if symptoms began many hours prior, as the possibility of intervention may still exist.

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