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Letter to Editor

Endovascular Therapy is now Established in Large Core Ischemia, but are we Cautious Enough?

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DEAR EDITOR

"Ischemic core" refers to the early phase of acute stroke when tissue fate is not yet 100% determined on baseline imaging. We commonly define "core" either as (1) brain tissue that is already infarcted at the time of evaluation or (2) tissue that, even if still potentially viable, is invariably destined to become infarcted regardless of treatment.

However, recent endovascular therapy (EVT) results in acute stroke appear to refute the traditional core/penumbra model. If large cores truly represented “dead brain,” reperfusion should not have helped.

Core estimates may not be fully accurate. Early edema and imaging artifacts can exaggerate infarct size (called a “ghost core”). Cores may not be homogeneous. Within the damaged region, there may be pockets of still-viable penumbra (“minipenumbras”). Patient variability matters. Some individuals (so-called “slow progressors”) maintain more viable tissue for longer due to collateral circulation. Even brain tissue with cerebral blood flow (CBF) as low as 5 mililite/100 g/min can regain function if CBF is augmented within 30 minutes [1].

Large core ischemia is defined as a significant volume of injured brain tissue in an acute stroke of ⩾50 millilitres via imaging (CTP or MRI) with severe perfusion deficits (e.g., cerebral blood flow <30%) or an ASPECTS score (<6). ASPECTS (Alberta Stroke Program Early CT Score), though an indispensable method, has significant limitations: it has less sensitivity for "early ischemic changes" (can be as low as 44%), does not truly reflect the volume and degree of the parenchyma involvement, is hard to differentiate acute ischemia from chronic infarcts/age-related white matter changes/pre-existing atrophy, especially in older patients, and has limitations for artifacts. All these indicate that a large core as determined by ASPECTS scoring may not always be true, and we may miss potential patients whom we can help by endovascular therapy.

According to the latest landmark trials, the RESCUE-JAPAN LIMIT, TENSION, SELECT-2 study, and ANGEL-ASPECTS study, timely EVT in large core ischaemic insults is a saviour. There is now strong evidence of EVT in patients with a large ischemic core (ASPECTS 3–5) on initial imaging who have excellent pre-stroke functional status (mRS 0–1) and substantial stroke severity (NIHSS ≥6) with occlusion of the internal carotid artery or proximal middle cerebral artery.

But we need not forget EVT has its own limitations: 1. Reperfusion of a large, damaged core increases the risk of bleeding into the infarcted area, which can worsen outcomes. 2. Restoring blood flow can paradoxically harm neurons through calcium overload, oxidative stress, and inflammation, leading to cell death. 3. Procedural Complications: risks include vessel dissection, perforation, device issues, and clot embolization to new territory.

These landmark trials also had their limitations in addition to the common drawbacks:

1. Less than 25% of ANGEL-ASPECTS participants were beyond 12 hours last known

well, and less than 25% of SELECT2 and TESLA participants were beyond 16 hours last known well (indicating more patients were selected in the earlier half of the stipulated inclusion time).
2. Only 16.6% of participants of the trials included patients who had larger core volumes of more than 150 millilitres [2]
3. There is a possibility that those within 4.5 hours of last known normal were offered intravenous thrombolysis less frequently in these trials, thereby influencing the results [2].
4. There is underrepresentation of the elderly group (more than 80 years) in these studies [2].

In an Indian study of EVT in large core ischemic strokes, 36% of patients reached mRS 0–3 at 90 days, which was similar to the RESCUE-JAPAN, LIMIT, TENSION, and SELECT-2 study results of 31% and 37.9%, respectively, but there was a 16% rate of symptomatic intracerebral hemorrhage (SICH) [3].

It is worth mentioning that the rate of SICH was higher in the aforementioned Asian trials, such as RESCUE-JAPAN LIMIT (9%) and ANGEL-ASPECTS (6.1%), compared to similar patients in other continents. Asian patients often exhibit higher blood levels of active metabolites from antiplatelet drugs and greater inhibition of platelet aggregation, leading to increased bleeding. Their lower average body weight and higher prevalence of hypertension contribute to increased bleeding risk. A higher prevalence of intracranial atherosclerosis (ICAS) in Asian patients with higher rates of re-occlusion requiring multiple attempts for recanalization, often demanding additional rescue treatments, including tirofiban infusion or intracranial stenting, may increase the risk of complications, indicating additional caution in this group of the population.

Besides this, careful consideration of EVT is required in large ischemic cores in elderly patients (≥75 or 80 years who often have universally poor outcomes, especially those with mRS > 3), significant background comorbidities with high HASBLED scores, advanced malignancy, patients with mRS of 4-5, background coagulation abnormalities with a history of intracranial bleed/recurrent systemic bleeding episodes, those with advanced vasculitis or having unwanted delay in initiation of the procedure in the late window setting (every 30-min delay in mechanical thrombectomy decreases favourable outcomes by 11%).

We also need to keep in mind important biological, metabolic, and radiological parameters during patient selection. This is because the outcome may be guarded in certain cases despite successful recanalization. The involvement of the corticospinal tract or specific brain regions (e.g., motor cortex), preoperative hyperglycemia, elevated platelet count, and most importantly, poor collateral scoring in multiphasic CT scans can be predictive of poor functional outcomes [4, 5].

In the time of crisis, the decision-making is difficult for the patients' family members. When they come to know the option of a high cost and a high-end procedure, their expectations rise high. More public awareness programs are required so that patients' families are aware of such recommended treatments and can make their decisions as soon as possible. But the treating team and patient's family should have practical expectations for the outcomes—this is because a high-end and costly procedure does not guarantee excellent outcomes.

Thus, guidelines are not groundlines, and there is individual uniqueness. We need personalized treatment decisions and family counselling. Utilization of optimized periprocedural care (including optimized blood pressure management), use of advanced catheters for the procedure, and careful postprocedural monitoring are required to ensure the best possible outcome.

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