Anesthetic Care for Acute Ischemic Stroke: Facts and Aspirations
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Stroke is currently the fourth leading cause of death in the United States (US), and by 2030, an estimated 3.9% of the US population over the age of 18 will have had a stroke, with direct medical costs of $184 billion in addition to $57 billion in lost productivity (1). In the US, the current standard for the treatment of acute ischemic stroke (AIS) is the intravenous administration of recombinant tissue plasminogen activator (rt-PA) if the patient presents within 4.5 hours of symptom onset. Less than 10% of all ischemic stroke patients can be treated with rtPA and of those treated only 1/3 recover with no or minimal disability (2, 3). Efforts to combine rtPA with neuroprotective therapeutics such as magnesium have been unsuccessful to date (3). rtPA has significant morbidities predominantly related to intracranial and extracranial hemorrhage (4) and has very limited ability to recanalize occluded large proximal cerebral arteries (5). Patients with large vessel ischemic stroke treated with intravenous rtPA achieve recanalization of the vessel only ~33% of the time (6, 7) and <10% recover with no or minimal disability (6).

Mechanical/Endovascular Recanalization—a Re-Emerging Horizon

Given the limitations of intravenous rtPA, there has been intense interest in developing endovascular interventions to locally recanalize blocked vessels, with hope for the successes seen in treating acute myocardial infarction. Previous randomized control trials (RCTs) have failed to find benefit in endovascular thrombolysis (either mechanical clot extraction or intra-arterial thrombolysis) as compared with intravenous thrombolytic administration (8). However, there have been great advances in the engineering of neuroendovascular devices over the past decade and modern ‘stent-retrievers’ have shown superiority over older clot-extraction devices (9). Simultaneously, the availability of rapid computerized tomography (CT) angiography technology has become more widespread, allowing early definitive identification of patients with cerebral large vessel occlusion.

Now, in 2015, the tide has turned following the publication of five RCTs (6-8, 10, 11). The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) (6) was the first to show improved functional outcomes associated with mechanical recanalization. Over 80% of patients in the endovascular therapy group were treated with stent retrievers. The intra-arterial intervention group had a 75.4% recanalization rate and 32.6% rate of functional independence at 90 days (modified Rankin Scale [mRS] score of 0-2). Both results were significantly better than the 32.9% recanalization rate and 19.1% rate of functional independence at 90 days in the control group (6).

Following the positive results of the MR CLEAN trial, two other ongoing RCTs initiated unplanned interim analyses and found sufficient benefits associated with endovascular thrombectomy for which both trials were terminated early (7, 12). In addition to finding even larger differences in functional independence favoring endovascular treatment than seen in the MR CLEAN trial, one trial was the first to show a mortality benefit (7). The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial demonstrated a 53.0% rate of functional independence at 90 days versus 29.3% in the control group (P<0.001) (7). The Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial (EXTEND-IA) trial added CT-perfusion imaging to the inclusion criteria, enrolling patients with large vessel occlusion and a <70 ml ischemic core...
with evidence of salvageable cerebral tissue (12). Functional independence at 90 days was 71% in the endovascular group compared to 40% in the rtPA group (P=0.01).

These results represent a sea change in AIS therapy. While there are still large groups of stroke patients who do not meet treatment eligibility criteria for acute endovascular therapy, those who do should reap great benefit and we should expect the number of endovascular interventions to increase progressively over time. As anesthesiologists, we are often emergently consulted to care for these patients undergoing endovascular therapy. How can we work to optimize outcomes?

**General Anesthesia versus Monitored Anesthesia Care for Mechanical Recanalization: Which is Better?**

With the increasing utilization of mechanical recanalization for large vessel AIS in the near future, there is a need for a better understanding of the factors affecting patient outcomes, including anesthetic technique. To date, there have been no prospective RCTs examining the impact of anesthetic type on this procedure. However, data from multiple retrospective studies show a correlation between the use of general anesthesia (GA) and worse outcome. For example, one multicenter study showed that GA was associated with worse functional outcomes as assessed by the mRS than monitored anesthesia care (MAC), based on data from 980 patients who underwent mechanical recanalization (13). Other retrospective studies have come to similar conclusions, with GA associated with worse functional outcomes (i.e., a mRS score >2) (14, 15), parenchymal hemorrhage (16), and higher in-hospital mortality (16). A recent meta-analysis of nine studies with 1956 patients found that GA had a lower odds ratio (OR) for good functional outcome (OR = 0.43; P < 0.01) and successful recanalization (OR = 0.49; P < 0.01), and a higher OR for mortality (OR = 2.59; P < 0.01) and respiratory complications (OR = 2.09; P < 0.01) (17). In the recent MR CLEAN trial, 37.8% of endovascular patients underwent GA at the request of the endovascular surgeon (6). According to the recently published data, GA was associated with delay to treatment initiation and an overall worse outcome compared to that without GA (18).

It is important to point out that there is a preference toward GA amongst endovascular interventionalists (19). Therefore, the anesthesiologist is frequently requested to specifically provide GA. At centers where there is an algorithm for selecting GA patients, the sicker and more severely impaired patients will likely be selected for GA. Patients receiving GA may harbor a cerebral infarct that is more extensive and advanced, are unable to cooperate or protect their airways, or have other major comorbidities. Indeed, in many of these retrospective studies, patients receiving GA had higher pre-procedural National Institutes of Health Stroke Scale (NIHSS) scores, indicating that they had more symptomatic strokes prior to endovascular intervention (13-15). The difference in baseline neurological status is an independent predictor of worse outcomes, including death (14, 16). However, the association between anesthesia technique and outcomes still remains after correcting for baseline stroke severity (NIHSS score) (14, 16).

**The Potential Benefits of Monitored Anesthesia Care: Why?**

There have been multiple explanations for the observed differences in outcomes with different anesthetic techniques (20). One argument is that the induction of GA leads to a decrease in blood pressure, which worsens the cerebral ischemia. Retrospective analyses of the hemodynamic parameters of patients underwent mechanical recanalization for AIS found that GA was associated with a lower minimum systolic, diastolic, and mean blood pressure than MAC, and that higher systolic blood pressure was associated with better outcomes (21). Other studies, however, have not found significant trends in hemodynamic variation between GA and MAC (16).

Taking into consideration the adage "time is brain", the differing outcomes between GA and MAC may also be due to time delays in achieving recanalization of the blocked vessels. The data on the time used for anesthesia preparation have been mixed, with some studies showing GA taking a longer time from the start of the case to groin puncture (16) while others showing MAC taking longer (15), and still other studies finding no significant differences in the time needed before the first incision...
Even studies that found a significant difference between GA and MAC in the time from the start of anesthesia to recanalization did not find a significant association with primary outcomes in the multivariate analysis (16).

In addition to hemodynamic and time delay issues, there are other compelling reasons why MAC might be preferred over GA. For one, neuro-interventionalists and anesthesiologists would be able to monitor neurological status throughout the procedure, potentially allowing them to more quickly detect complications such as hemorrhage or allowing the procedure to be terminated after neurologic improvement rather than angiographic recanalization. Secondly, MAC avoids hazards associated with intubation and mechanical ventilation, including the placement of a patient on a so-called 'critical care treatment pathway' (22). Finally, MAC typically involves low-dose propofol or other intravenous anesthetic infusions. Whether the choice and dose of drugs contribute to the beneficial outcomes associated with MAC is unknown.

Nonetheless, MAC has its own risks. The airway without a cuffed endotracheal tube is threatened by aspiration in the setting of a full stomach or altered mental status. Desaturation can occur secondary to airway obstruction and mandate emergent airway intervention mid-procedure. In addition, an uncooperative or moving patient may have a higher risk of procedural complications such as vascular perforation, prolonged intervention, and delayed or impossible clot extraction.

**Clinical Implications & Conclusions**

Despite the accumulating evidence suggesting improved outcomes with MAC compared with GA for the mechanical recanalization of large vessel AIS, there are still many questions that need to be addressed. First and foremost, there is a need for robust RCTs. Two randomized studies are currently underway in Europe examining the outcome associated with GA versus MAC in this patient population (ANSTROKE: https://clinicaltrials.gov/ct2/show/NCT01872884; and GOLIATH: https://clinicaltrials.gov/ct2/show/NCT02317237). There is also a paucity of data on the anesthetic agents used for anesthesia induction and maintenance, which may be important given the different effects of anesthetics on the cerebral circulation (20).

The most recent expert consensus from the Society of Neuroscience in Anesthesia and Critical Care recommends an individualized approach, based on each patient’s clinical characteristics coupled with the procedural needs of the neuro-interventionalists, when choosing the anesthetic technique and pharmacological agents for the procedure. GA remains preferable in patients who cannot protect their airway and MAC is preferable in patients who can protect their airway and are cooperative (class IIa, level B evidence) (22). If GA is chosen for all patients at a given institution based on the preference of the neuro-interventionalists, the patients should be exhaled as soon as possible following the procedure. Every effort should be made to minimize time delays, have institutional pathways for providing anesthesia services with great efficiency, and maintain adequate cerebral perfusion pressure during the procedure.

We caution that the debate on anesthetic technique in endovascular stroke therapy may not be settled even when RCT results become available. These studies can only include patients who are candidates for both GA and MAC prior to randomization because it would be unethical to initiate MAC in a patient who is confused, agitated, or has a compromised airway. Therefore, a pragmatic scale that can efficiently and effectively assess the overall anesthetic and procedural risks in a fast-paced care setting is needed to facilitate interdisciplinary communication, risk stratification, and decision making. All in all, the improvements in endovascular therapy represent a great leap forward for ischemic stroke patients. For anesthesiologists, this fragile and growing patient population represents a tremendous opportunity to facilitate life-saving therapy while optimizing outcomes with carefully crafted anesthetic care.

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