Anesthesia for endovascular treatment of acute ischemic stroke

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ABSTRACT

The initial treatment of patients with acute ischemic stroke (AIS) focuses on rapid recanalization, which often includes the use of endovascular therapies. Endovascular treatment depends upon micromanipulation of catheters and devices into the cerebral vasculature, which is easier and safer with a motionless patient. Unfortunately, many stroke patients are unable to communicate and sufficiently cooperate with the procedure. Thus, general anesthesia (GA) with endotracheal intubation provides an attractive means of keeping the patient comfortable and motionless during a procedure that could otherwise be lengthy and uncomfortable. However, several recent retrospective studies have shown an association between GA and poorer outcomes in comparison with conscious sedation for endovascular treatment of AIS, though prospective studies are lacking. The underlying reasons why GA might produce a worse outcome are unknown but may include hemodynamic instability and hypotension, delays in treatment, prolonged intubation with or without neuromuscular blockade, or even neurotoxicity of the anesthetic agent itself. Currently, the choice between GA and conscious sedation should be tailored to the individual patient, on the basis of neurologic deficits, airway and hemodynamic status, and treatment plan. The use of institutional treatment protocols may best support efficient and effective care for AIS patients undergoing endovascular therapy. Important components of such protocols would include parameters to choose anesthetic modality, timeliness of induction, blood pressure goals, minimization of neuromuscular blockade, and planned extubation at the end of the procedure. Neurology® 2012;79 (Suppl 1):S167–S173

GLOSSARY

AIS = acute ischemic stroke; CI = confidence interval; CS = conscious sedation; GA = general anesthesia; OR = odds ratio; tPA = tissue plasminogen activator.

The goal of early therapy for acute ischemic stroke (AIS) is to restore perfusion to ischemic areas of the brain. The introduction of IV fibrinolysis was a tremendous step forward in emergency patient care.1 However, despite current professional education programs, enhanced public awareness, and integrated stroke care, only 3% to 8.5% of stroke patients are treated with IV tissue plasminogen activator (tPA).2 Furthermore, fewer than half of patients with large-artery occlusions who are treated with tPA experience recanalization from thrombolysis.3 Thus, there is a need for additional reperfusion strategies.

Endovascular therapy offers a more direct approach to the occlusive lesion. Furlan et al.4 initially showed that the intra-arterial administration of thrombolytics led to improved outcomes in patients with large-artery occlusions. Later, mechanical thrombectomy was shown to be more effective in terms of recanalization,5,6 with more recent success rates of 81% to 84%.7 Currently, there are an array of endovascular treatment options, including intra-arterial pharmacologic fibrinolysis, guidewire maceration, clot retrieval, thrombus aspiration, angioplasty, and stenting. Choosing from the available options for endovascular stroke treatment is difficult and is usually made on a case-by-case basis, as there are often important technical differences.

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between devices and their use. For example, some devices may require more precision in their deployment, others may cause more patient discomfort, and some may require longer procedure times.

Patients with stroke often have significant neurologic impairment; they may be aphasic and unable to communicate, may be paretic, or may experience vertigo—any of which may cause significant distress. This can make it difficult for the patient to tolerate a procedure that requires lying still for a prolonged period of time. And if the patient is unable to remain motionless, it can cause significant degradation in image quality, inability to utilize roadmap functions, and even trauma and vessel damage related to movement of the catheter. To address these considerations, anesthesia is often utilized in neurointervention. Anesthesia may come in the form of conscious sedation (CS), with administration of low-dose analgesics and hypnotics that may improve the comfort of the patient but may not be adequate to fully immobilize the patient. General anesthesia (GA) with endotracheal intubation allows for a completely motionless patient but may be associated with significant disadvantages.

In particular, several recent studies have demonstrated worse outcomes after endovascular treatment in AIS patients with GA, in comparison with CS.\(^\text{8–10}\) If this finding is true, then the choice of anesthesia during acute stroke treatment may have important ramifications. Thus, we shall first review the recent clinical data, before speculating on the potential mechanisms underlying worse outcomes with GA, which might include hemodynamic changes, neurotoxicity, delays in treatment, or prolonged intubation. A better understanding of these and other considerations should allow the development of rational protocols for the use of anesthesia in patients with AIS.

Clinical studies. There have been no prospective, randomized studies comparing GA with CS in endovascular treatment of AIS or of any other cerebrovascular disease. However, several recently published retrospective studies have provided some compelling data and ignited considerable debate on this issue.\(^\text{11,12}\)

Currently, it appears that endovascular neurologists are mixed in their use of GA vs CS for patients undergoing interventional therapy for AIS. In a recent survey of the members of the Society of Vascular and Interventional Neurologists, McDonagh et al.\(^\text{13}\) found that only 6% of the respondents used GA exclusively. However, 55% of respondents believed that GA is mandatory when using mechanical thrombectomy. This preference for GA was based on the assumption that limiting movement makes the interventional procedure safer and more efficacious. Although GA and immobility allow greater image quality and decrease procedural time, the greatest perceived limitation was a delay in starting the procedure.

The relationship between periprocedural sedation and outcome has been assessed by 3 recent studies. Nichols et al.\(^\text{8}\) studied the sedation practices in the Interventional Management of Stroke II Trial. Of 81 patients, sedation data were available for 75. A sedation classification scale was used to classify the extent of sedation used: 1 = no sedation, 2 = mild sedation, 3 = heavy sedation, and 4 = pharmacologic paralysis. Fifty-three percent (\(n = 40\)) were given no sedation (grade 1) and 23% (\(n = 17\)) were intubated paralyzed (grade 4). Patients in the higher sedation categories had higher baseline NIH Stroke Scale scores, suggesting more severe baseline stroke severity. Patients in lower sedation categories had better outcomes, more frequent reperfusion rates, and lower mortality. When accounting for baseline neurologic status with use of multivariate analysis, mild or no sedation (grade 1 or 2) was associated with a good clinical outcome (odds ratio [OR] 5.7; 95% confidence interval [CI] 1.5–12.3), and heavy sedation or paralysis (grade 3 or 4) was an independent predictor of death (OR 5.0; 95% CI 1.3–18.7).

Jumaa et al.\(^\text{9}\) retrospectively reviewed 126 patients who had received endovascular therapy for AIS due to middle cerebral artery occlusion. Level of sedation was classified as intubated (42%) vs nonintubated (58%). Nonintubation was associated with shorter ICU stays (3.2 vs 6.5 days; \(p = 0.0008\)), lower infarct volume (OR 0.25; \(p = 0.004\)), good clinical outcome (OR 3.06; \(p = 0.042\)), and lower in-hospital mortality (OR 0.32; \(p = 0.011\)). A nonsignificant difference in complications was observed, with 6% in the intubated group and 15% in the nonintubated group (\(p = 0.13\)).

The largest study was performed by Abou-Chebl et al.,\(^\text{10}\) who recently reported the results of a multicenter, retrospective review of 980 endovascular acute stroke cases. GA was used in 44% of all patients, and these patients were more likely to have carotid terminus occlusions and higher NIH Stroke Scale scores. The intracranial hemorrhage rate was no differ-
ent between GA and CS. However, GA was an independent predictor of poor neurologic outcome (OR 2.33; 95% CI 1.63–3.44) and higher mortality (OR 1.68; 95% CI 1.23–2.30) in multivariate analyses.

Limited published data suggest that CS may be adequate and safe in patients undergoing neurointerventional procedures for diseases other than AIS. Ogilvy et al.\textsuperscript{14} reported using CS in 92.2% of elective aneurysm embolizations in 340 patients, with low morbidity and mortality rates and short hospital stays. Additionally, complications and effectiveness were similar between GA and CS among patients undergoing angioplasty and stenting for intracranial stenosis.\textsuperscript{15} Of course, patients undergoing these elective treatments are typically much more comfortable and cooperative than patients with AIS, and these procedures are not performed in the emergent setting. Nonetheless, these reports highlight the feasibility of performing neurointerventional procedures in the nonanesthetized patient.

These retrospective data provide some evidence that outcomes in endovascular treatment of AIS may be worse with the use of GA. Of course, prospective data will be needed to definitively address this issue, although recruitment in a randomized trial may be difficult. But if the current data from these 3 trials are accurate, what might be the reason for the difference in outcomes between GA and CS? Some possibilities might include hemodynamic changes, delays in treatment, prolonged intubation, neuromuscular blockade, and neurotoxicity of the anesthetic agents themselves.

**Hemodynamic effects of GA.** GA has a range of systemic and cerebral effects, but probably the most unwelcome effect in acute stroke is hypotension. In the setting of AIS, an occluded artery causes focal cerebral ischemia, and a reduction in systemic blood pressure (cerebral perfusion pressure) may lead to reduction in collateral perfusion,\textsuperscript{16} which could hasten the progression to complete infarction.\textsuperscript{17} Typically, the most pronounced drop in blood pressure occurs immediately after induction. This decline in blood pressure is associated with lower baseline blood pressure, the use of certain anesthetic agents, and general health status.\textsuperscript{18} Postinduction hypotension, even in elective surgery, has been associated with prolonged hospital stays and increased mortality.\textsuperscript{18} Thus, when GA is used in acute stroke patients, blood pressure should be strictly controlled, particularly at the time of induction, with use of predefined parameters but accounting for the baseline blood pressure, stroke syndrome, and the patient’s general health status.

In particular, the patient’s baseline blood pressure is of critical importance, as cerebral blood flow is autoregulated only within a limited range, and hypotension beyond this range can lead to cerebral ischemia, especially in the setting of stroke and decreased collateral availability. Therefore, any blood pressure reduction at the time of anesthesia induction could impair potentially important collateral perfusion. The safest approach given the unknown level of risk with blood pressure reduction is to assume that the patient has tenuous collateral perfusion and to keep the blood pressure at the preinduction baseline. In practical terms, this translates into maintaining hypertension during the AIS intervention.

Although all anesthetic agents cause some hypotension, they vary in their effects on the cerebral vasculature and intracranial pressure. Specifically, the halogenated inhalational anesthetic agents (isoflurane, sevoflurane, and desflurane) are cerebral vasodilators and do not maintain the normal coupling of cerebral blood flow with cerebral metabolic rate.\textsuperscript{19–21} Thus, although they suppress the cerebral metabolic rate, they cause a relative cerebral hyperemia. This can be a significant concern in patients with elevated intracranial pressure, although not in the majority of AIS patients who have normal intracranial pressure. It should be noted that controlled ventilation with hypocapnia can offset this vasodilatory effect of the halogenated inhaled anesthetics.\textsuperscript{22}

In contrast to the halogenated agents, propofol better preserves cerebral autoregulation.\textsuperscript{19,23} Therefore, as the cerebral metabolic rate is reduced with propofol, the cerebral blood volume is reduced proportionally. Nitrous oxide should be avoided in acute stroke interventions because of concerns for exacerbating any cerebrovascular air emboli entrained during the procedure.\textsuperscript{24,25}

Both the halogenated anesthetic agents and propofol cause dose-dependent systemic hypotension due to vasodilatation,\textsuperscript{21,24} which is particularly pronounced at the time of induction. Propofol causes more hypotension postinduction than other induction agents such as etomidate,\textsuperscript{18} whose use may be preferred in the setting of AIS. This drop in cerebral perfusion pressure often necessitates the concomitant use of vasopressor agents. Unfortunately, we have no adequate point-of-care cerebral perfusion monitors to guide hemodynamic therapies intraoperatively during AIS interventions. Therefore, it is critical to determine blood pressure parameters before induction and to rapidly correct hypotension with pressors, on the basis of predefined blood pressure goals. Finally, other factors that could further contribute to excessive vasoconstriction or vasodilation, such as hypocapnia or hypercapnia, should be avoided.

Analgesia is an important component of GA and of CS. An opioid is typically employed for this purpose, and short-acting opioids such as remifentanil,
because of its lack of accumulation (i.e., lack of context sensitivity), are well suited to acute stroke interventions. Hypotension is again a side effect that must be monitored closely and counteracted with pressor agents such as phenylephrine, norepinephrine, or ephedrine.

**Logistical considerations.** The emergent delivery of endovascular therapy to an occluded intracranial vessel requires an efficient health care delivery system involving multiple clinical services within the hospital working together. Orchestrating care among the emergency department, imaging, stroke team, and interventional service can be challenging and time-consuming. The immediate availability of an experienced anesthesia team to provide care for patients as a Level 1 emergency is important. Unfortunately, this is not always the case in many centers. The endovascular suite is commonly located apart from main operating rooms, stretching the capability of the anesthesia team to rapidly respond, particularly at times when staffing levels are limited. The equipment and medications required for delivery of anesthetic care should be readily accessible within the neurointerventional area. Any factor that leads to a delay in the initiation of the procedure is detrimental. The familiarity of the anesthesia team with acute stroke intervention and the endovascular suite environment can vary significantly, especially during off hours. Therefore, discussion of parameters such as blood pressure goals and foreseeable time course for anesthetic induction and endotracheal intubation should take place in advance.

CS is commonly used in many centers worldwide for AIS interventions. However, various concerns arise with the use of CS. The optimal management of sedation to produce a cooperative, nonmoving patient varies in difficulty from patient to patient. In addition, patients have typically not fasted as they would for an elective cerebral endovascular procedure. This raises concerns for pulmonary aspiration of gastric contents in the setting of sedation and supine positioning. The need for emergent endotracheal intubation may result from any combination of oversedation, neurologic decline, airway compromise, or agitation. Emergent conversion to GA during the endovascular procedure may result in hypoxia or aspiration and necessitates the presence of a practitioner skilled in endotracheal intubation.

General anesthesia is a logical and seemingly attractive solution to many of these issues, since the patient will be deeply sedated with a protected airway (endotracheal intubation). However, there are potentially significant downsides. As discussed, the use of GA must not delay the delivery of reperfusion therapy. In addition, there is a loss of the neurologic examination and the procedure must proceed to a radiographic endpoint rather than a clinical endpoint. As discussed above, the requirement for endotracheal intubation during GA has been associated with longer intensive care unit stays, pneumonia, and increased mortality in retrospective studies. This may be due in part to the transport of patients to the intensive care unit while intubated after the procedure, leaving the weaning to occur at a later time. Development of ventilator-associated pneumonia is known to increase with longer duration of intubation. Extubation immediately after the procedure to allow for neurologic examination and avoid potential complications should be the goal when possible.

**Procedural paralysis.** The endovascular procedure requires minimal patient movement for safe, efficient delivery of catheters and devices for thrombolysis and thrombectomy, for 2 major reasons. First, patient motion creates imaging artifact, resulting in angiographic images that are difficult to interpret. Time lost repeating imaging to obtain a clear picture of the anatomy and occlusion site can add up to significant delays. Second, patient motion during critical parts of the procedure while mechanical instrumentation is in the cerebral vasculature can lead to devastating complications. For the purposes of minimizing patient motion, GA is superior to CS or monitored anesthesia care.

Anesthesiologists utilize neuromuscular blocking agents to facilitate endotracheal intubation and provide a margin of safety during these procedures, allowing optimal visualization of the cervical and intracranial vasculature. For the acute stroke patient in whom a neurologic examination is often desired immediately after the procedure, the neuromuscular blocking agent used should be readily reversible. Intermediate-acting agents such as cisatracurium, vecuronium, and rocuronium are preferred. Depth of neuromuscular blockade should be monitored during the procedure so that reversal of the blockade can be performed at the end of the procedure and ongoing endotracheal intubation can be avoided. In addition, older agents such as atracurium, which is associated with histamine release (causing hypotension and decreased cerebral perfusion pressure), should be avoided.

**Anesthetic neuroprotection or neurotoxicity?** To add further complexity to the question of GA in AIS interventions, we must consider longer-term effects of the anesthetic agents themselves. There is a large literature on the neuroprotective effects of anesthetic agents, spanning 3 decades, mostly relating to the barbiturates and isoflurane. In fact, there is strong evidence for the neuroprotective effect of isoflurane in rodent models of
focal ischemia (i.e., acute stroke).\textsuperscript{31} Human trials of barbiturate neuroprotection after cardiac arrest\textsuperscript{32} were negative, but no human evidence exists for the neuroprotective or neurotoxic effects of general anesthetics in acute ischemic stroke.

More recently, concern has grown regarding the potential neurotoxic effects of anesthetics, particularly isoflurane.\textsuperscript{33–36} There is evidence from cell culture and rodent models that isoflurane promotes oligomerization of \( \beta \)-amyloid, one of the pathophysiologic processes in Alzheimer disease, and causes neurotoxicity in both neonatal and elderly animals.\textsuperscript{33–34} Nitrous oxide and ketamine have also been implicated, and data from animal studies indicate that toxicity may be mediated by NMDA receptor antagonist (e.g., ketamine)–induced vacuolization of neurons of adult and aged rodents.\textsuperscript{35,36} Human studies are under way in at-risk populations.

To our knowledge, there are no data to date regarding anesthetic neurotoxicity in acute ischemic stroke. Whether common perioperative neurologic complications such as delirium and postoperative cognitive dysfunction are related to anesthetic neurotoxicity or other factors is similarly unknown.\textsuperscript{37}

It will be difficult to directly study the neuroprotective or neurotoxic effects of general anesthetics in patients with AIS. However, outcome studies in ischemic stroke populations are needed to define the short-term and long-term impact of general anesthetics on the nervous system. In addition, animal stroke models should also be utilized to explore the potential mechanisms of neurotoxicity of anesthetic agents.

As an aside, the discussion of neuroprotection would be incomplete without considering therapeutic hypothermia. The use of GA for AIS interventions would facilitate the rapid induction of therapeutic hypothermia. However, to date, only early stage feasibility trials have been conducted,\textsuperscript{38} and there is currently no convincing human evidence to suggest that AIS patients benefit from cooling. Current goals are to maintain normothermia, while avoiding hypothermia, in AIS interventions.

**DISCUSSION** Acute stroke therapy has evolved significantly. Entire systems of care have developed to support the delivery of recanalization therapies, which have included physician, hospital, corporate, and legislative efforts.\textsuperscript{39,40} Although these systems have certainly improved the structure of care and resources available to those of us who treat ischemic stroke, the treatment of each individual patient still brings new challenges to the rapid delivery of appropriate therapy. One such challenge is the decision regarding anesthesia for AIS patients undergoing endovascular treatment. Making this decision involves an assessment of neurologic status, airway, ability to cooperate with the procedure, anticipated technique and procedure time, planned postprocedure care, and other factors. And beyond these individual patient factors, we must consider the general risks of GA, including delay to treatment, hemodynamic instability, and the loss of the neurologic examination during the procedure. In light of recent data, we must also consider the possibility that the use of GA may be associated with poorer outcomes. Randomized controlled trials of the use of GA in AIS interventions would provide the highest level of evidence to guide therapy. However, in the interim, the inclusion of sedation type, factors influencing choice of sedation, and complications related to sedative modality should be prospectively gathered in any AIS intervention trials. This will provide intermediate-level evidence that is superior to what is currently available in regard to the impact of GA on outcome after AIS interventions.

Until we have better evidence to guide us, we must individualize choice of anesthesia to each patient. GA may be more appropriate for patients with severe deficits, airway compromise, or bulbar dysfunction. CS may be more appropriate for patients with milder deficits or those with tenuous hemodynamic status. To minimize the potentially negative effects of GA with endotracheal intubation, the neurointerventional and anesthesiologist should plan to extubate at the end of the case unless there is a contraindication, and agree upon hemodynamic parameters before the start of the case. Ideally, these goals would be supported by institutional treatment protocols that would avoid the need for lengthy planning and discussion prior to the start of each case. Indeed, the use of GA vs CS can be based on a protocol that incorporates clinical status, anticipated procedural technique, and planned postprocedure care. The use of standardized protocols in treating for ischemic stroke patients does improve their care,\textsuperscript{39} and we would advocate the use of an anesthesia protocol to further support safe and efficient endovascular treatment for patients with AIS.

**AUTHOR CONTRIBUTIONS**

Dr. Froehler and Dr. Fifi: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Majid: drafting/revising the manuscript, Dr. Bhatt and Dr. Ouyang: drafting/revising the manuscript, study supervision. Dr. McDonagh: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data.

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