Impact of General Anesthesia on Safety and Outcomes in the Endovascular Arm of Interventional Management of Stroke (IMS) III Trial

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Background and Purpose—General anesthesia (GA) for endovascular therapy (EVT) of acute ischemic stroke may be associated with worse outcomes.

Methods—The Interventional Management of Stroke III trial randomized patients within 3 hours of acute ischemic stroke onset to intravenous tissue-type plasminogen activator±EVT. GA use within 7 hours of stroke onset was recorded per protocol. Good outcome was defined as 90-day modified Rankin Scale ≤2. A multivariable analysis adjusting for dichotomized National Institutes of Health Stroke Scale (NIHSS; 8–19 versus ≥20), age, and time from onset to groin puncture was performed.

Results—Four hundred thirty-four patients were randomized to EVT, 269 (62%) were treated under local anesthesia and 147 (33.9%) under GA; 18 (4%) were undetermined. The 2 groups were comparable except for median baseline NIHSS (16 local anesthesia versus 18 GA; P=0.0001). The GA group was less likely to achieve a good outcome (adjusted relative risk, 0.68; confidence interval, 0.52–0.90; P=0.0056) and had increased in-hospital mortality (adjusted relative risk, 2.84; confidence interval, 1.65–4.91; P=0.0002). Those with medically indicated GA had worse outcomes (adjusted relative risk, 0.49; confidence interval, 0.30–0.81; P=0.005) and increased mortality (relative risk, 3.93; confidence interval, 2.18–7.10; P<0.0001) with a trend for higher mortality with routine GA. There was no significant difference in the adjusted risks of subarachnoid hemorrhage (P=0.32) or symptomatic intracerebral hemorrhage (P=0.37).

Conclusions—GA was associated with worse neurological outcomes and increased mortality in the EVT arm; this was primarily true among patients with medical indications for GA. Relative risk estimates, though not statistically significant, suggest reduced risk for subarachnoid hemorrhage and symptomatic intracerebral hemorrhage under local anesthesia. Although the reasons for these associations are not clear, these data support the use of local anesthesia when possible during EVT.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00359424.

Key Words: anesthesia ■ embolectomy ■ endovascular procedures ■ injections, intra-arterial ■ stroke ■ thrombolysis
the discrepancy between superior reperfusion and similar clinical outcomes, it is important to investigate factors associated with EVT that may positively or negatively affect clinical outcome. Although newer device technologies have garnered the majority of attention, another potentially important factor contributing to outcomes is periprocedural patient management, such as blood pressure (BP), glucose, and temperature management, all of which are linked with stroke outcomes. The choice of procedural anesthesia may also be important.

Several retrospective registries have shown worse outcomes in patients treated with EVT under general anesthesia (GA) when compared with local anesthesia (LA) or conscious sedation (will be collectively referred to as LA in this article). The largest of these was a multicenter retrospective study of 980 patients that found that GA was associated with poor outcome at 90 days and increased mortality. In a retrospective analysis of 75 patients from the IMS II study, patients treated with lesser degrees of anesthesia fared better with improved neurological outcomes and lower mortality. These data were retrospective and have been controversial as there are proponents of GA who cite increased safety during the procedure as the primary indication, although the retrospective data have shown that the risk of subarachnoid hemorrhage (SAH) or symptomatic intracerebral hemorrhage (sICH) has been equivalent or lower with LA.

The IMS III trial afforded an opportunity to study the possible impact of anesthesia on EVT outcomes in a planned analysis. The following primary hypotheses were tested in this study: (1) GA is associated with poorer outcomes, (2) there is a difference in the risk of SAH and sICH in patients undergoing GA compared with LA, and (3) GA is associated with longer time to EVT initiation.

Methods

The IMS III trial was a multicenter, randomized, open-label trial of EVT following intravenous thrombolysis in patients with moderate to severe acute ischemic stroke treated within 3 hours of stroke onset sponsored by the National Institute of Neurological Disorders and Stroke. The protocol, patient selection criteria, treatment approaches, and final results have been previously published. Randomization and analysis were stratified by severity, defined according to National Institutes of Health Stroke Scale (NIHSS) ≤19 or ≥20. The primary clinical outcome was a modified Rankin Scale (mRS) score of ≤2 at 90 days, performed by blinded investigators. Recanalization success was defined as a Thrombolysis in Cerebral Infarction (TICI) score ≥2. The primary safety end points were death, SAH, and sICH (defined as any intracranial hemorrhage within 24±6 hours of randomization temporally related to a decline in neurological status as well as new or worsening neurological symptoms in the judgment of the clinical investigator and which may have warranted medical intervention). Local institutional review board approval was obtained at all centers.

Periprocedural anesthesia was defined as GA if the subject underwent endotracheal intubation within 7 hours of stroke onset. This time period was chosen to capture all patients who were intubated before or during procedure because the protocol mandated initiation of the angiographic procedure within 5 hours and completion within 7 hours after stroke onset. All other EVT subjects were defined as having undergone LA, regardless of whether or not they received conscious sedation. Subjects were intubated based on the judgment of the treating team and not per protocol. The primary reason for intubation was categorized by each investigator as: (1) routine practice (ie, routine practice to intubate and use GA before EVT) or (2) medically indicated (ie, concern for ability to protect airway/aspiration risk, cardiopulmonary deterioration, signs of herniation/increased intracranial pressure, inadequate pain control or agitation, or other). The study protocol did not mandate one approach over the other. The endovascular approach was previously described.

Statistical Analysis

Subjects with intubation status unknown (n=18) were excluded from the analysis. For consistency with the primary publication, an unfavorable outcome was imputed for subjects with mRS missing or obtained outside of window. The generalized linear model was used to test the association between GA and outcome, with the log link used to produce relative risk estimates. Confidence intervals (CI) provided are 95% intervals. Because the limited sample size and small number of safety events, particularly with respect to sICH, limited the number of potential covariate adjustments, these were prespecified based on clinical relevance rather than selected according to statistical significance. For models of good outcome and in-hospital mortality, adjusted models included severity stratum, age, and time from onset to groin puncture (T_groin); models of safety outcomes were adjusted only for mechanical embolectomy. Procedural times are described via mean±SD; the effect of GA on these times is assessed via t test.

Results

A total of 434 patients were randomized to the EVT arm of IMS III. GA was used in 147 (33.9%) patients. The GA and LA cohorts were comparable in baseline demographics, medical comorbidities, time to tissue-type plasminogen activator (tPA), time from intravenous tPA initiation to EVT initiation, time from onset to recanalization, 40-minute post tPA bolus systolic BP, and occlusion side (Table 1). The LA cohort tended to have lower NIHSS scores (median 16 versus 18; P<0.0001) and slightly lower incidence of internal carotid artery occlusion (P=0.06). Intubation was associated with stroke severity as measured by NIHSS quartiles (≤14, 15–19, 20–24, ≥25; P value <0.0001) as well as by baseline Alberta Stroke Program Early CT Score (ASPECTS; P value=0.0395). Reperfusion success (TICI, 2–3) was achieved in 76.4% of the GA cohort versus 72.8% of the LA cohort, P=0.48 (Table 2). Good outcome was achieved in 129/269 (48.0%) LA patients and in 45/147 (30.6%) GA patients (Table 2). The GA group was significantly less likely to achieve a good outcome (relative risk [RR], 0.64; CI, 0.49–0.84; P=0.0013; Figure). There was a significant association between intubation and inhospital death with 23.1% (34/147) mortality in the GA cohort and 7.4% (20/269) in the LA cohort (RR, 3.11; CI, 1.86–5.20; P=0.0013) and in-hospital mortality (RR, 2.84; CI, 1.65–4.91; P=0.0002; Table 3). Compared with LA, medically indicated GA was associated with lower probability of a good outcome (adjusted RR, 0.49; CI, 0.30–0.81; P=0.005) and increased mortality (adjusted RR, 3.93; CI, 2.18–7.10; P<0.0001; Table 3). Differences between routine GA and LA subjects did not reach statistical significance for either good outcome (adjusted RR, 0.80; CI, 0.60–1.06; P=0.12) or mortality (adjusted RR, 1.82; CI, 0.87–3.77; P=0.11). There was higher in-hospital mortality among the medically indicated GA cohort than the routine cohort (adjusted RR, 2.16; CI, 1.09–4.29; P=0.0274).
but the difference in good outcomes did not reach significance (adjusted RR, 0.62; CI, 0.36–1.07; \(P=0.0840\)). The results were not substantively affected by adjusting for a more detailed severity designation (NIHSS \(\leq 14, 15–19, 20–24, \geq 25\)).

There was a significant association between GA and SAH (RR, 1.79; CI, 1.04–3.08; \(P=0.035\)). This relationship was confounded by endovascular approach. After adjustment for mechanical embolectomy, the association was not significant (adjusted RR, 1.34; CI, 0.76–2.38; \(P=0.32\)), Table 3. The association between GA and sICH did not reach statistical significance (RR, 1.69; CI, 0.79–3.61; \(P=0.18\)), even after adjustment for mechanical embolectomy (adjusted RR, 1.45; CI, 0.64–3.27; \(P=0.37\)).

An on treatment analysis by exclusion of the 97 (23.3%) patients in the EVT arm who did not receive any EVT did not significantly change the results. GA was still associated with reduction in good outcomes (RR, 0.53; \(P=0.0003\)) and an increase of in-hospital mortality (RR, 2.95; \(P<0.0001\)) but the
association with risk of SAH (RR, 1.45; P=0.21) or sICH (RR, 1.47; P=0.35) was not statistically significant. These findings were maintained after adjustment.

In both the unadjusted and adjusted analyses, there was insufficient evidence to conclude that there was a significant difference in good outcomes between the LA (48%) and routine GA (40.8%) cohorts compared with intravenous tPA alone (42.9%). However in-hospital mortality was significantly reduced in the LA cohort compared with intravenous therapy (adjusted RR, 0.56; CI, 0.33–0.97; P=0.0002). The medically indicated GA cohort had lower probability of good outcomes compared with intravenous therapy (adjusted RR, 0.57; CI, 0.35–0.93, P=0.0154) and significantly increased mortality (adjusted RR, 2.0; CI, 1.23–2.30; P<0.0001).

The exact reasons why GA seems to be associated with worse outcomes is likely multifactorial. One possibility is hemodynamic perturbations, especially hypotension associated with the induction of GA.10 In a retrospective single center study of 96 EVT patients, Davis et al11 found a negative association between GA use and good outcomes (15% probability of good outcomes versus 60% in the LA patients). They also found an association of good outcomes with systolic BP >140 mm Hg, the presence of which was negatively correlated with GA use, leading them to postulate that the deleterious effects of GA were because of the changes in systolic BP. This association is supported by another retrospective study of 216 EVT patients, 60% of whom were treated with GA and the remainder with conscious sedation using dexmedetomidine. This study found greater variations in BP in the GA group and that higher procedural BP was associated with better outcomes.12 In this current study, the closest preprocedural BP reading collected, the systolic BP 40 minutes after the initiation of intravenous tPA, was numerically higher in the LA cohort although the difference was not statistically significant. A higher preanesthesia BP could be associated with improved outcomes and could explain some of the findings in this study but that is purely conjectural because no other periprocedural readings were collected.11,12

Discussion

The use of GA in the EVT arm in the IMS III Trial was associated with worse neurological outcomes and increased mortality. There was a 17% absolute difference in the proportion of patients with good outcomes in favor of LA that remained essentially unchanged when adjusted for NIHSS severity stratum, age, and T0. In-hospital mortality was 3-fold higher in the GA group. The difference between GA and LA was primarily seen in subjects for whom GA was deemed medically necessary when compared with routine practice, although the trend lines for all outcomes and end points favored LA even compared with the routine GA patients. These differences in outcomes are clinically significant and consistent with the findings of recent retrospective series.5,6,9 The largest of these was a multicenter retrospective study of 980 IAT patients, 44% of whom were treated under GA.5 In that study, GA was associated with increased odds of poor outcome (mRS ≥3; odds ratio [OR], 2.33; 95% CI, 1.63–3.44; P<0.0001) and mortality (OR, 1.68; 95% CI, 1.23–2.30; P<0.0001).

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Figure. Distribution of modified Rankin Scale scores of disability at 3 months.
The mechanism by which reduction in BP could worsen outcomes is unknown but is likely via a reduction in cerebral blood flow to the ischemic penumbra potentiating the extent of injury. Additionally increases in cerebral venous pressure, which have been noted to occur with GA and endotracheal intubation, could potentiate the effect of lower BP. Future trials should study the effect of BP on outcomes and its possible interaction with type of anesthesia. There are theoretical concerns of neurotoxicity of certain anesthetic agents but only a prospective study comparing different agents can confirm or disprove this effect.

A major weakness of the retrospective studies published to date is that the reasons for initiating anesthesia were not known and the association between GA and poor outcomes could have been because of underlying medical comorbidities or stroke severity that necessitated GA. We attempted to control for as many factors as possible but the small number of events limited the number of variables that we could assess. Although the median NIHSS was slightly lower in the LA group, a finding seen in some of the earlier series, the difference in outcomes in favor of LA persisted after adjustment for the dichotomized severity stratum (NIHSS ≤19 versus ≥20). Davis et al also found that GA patients had more severe strokes than LA patients, but in their institution GA was reserved for patients who cannot cooperate and those with acute critical events, such as airway obstruction. In IMS III, we attempted to control for this variable by differentiating the GA cohort into those intubated as part of routine practice and those intubated because of a medical indication. The worst outcomes were in those who had a medical indication. This would suggest that sicker patients (ie, cardiopulmonary failure) do worse, perhaps because of their underlying medical conditions or an interaction with GA. However, the differences in medical comorbidities were not significant between the GA and LA cohorts. In addition, the GA patients tended to have higher NIHSS scores, but the differences were unlikely significant enough to account for the major differences in outcomes and a 3-fold higher mortality in the GA cohort compared with LA. A major limitation of this study is the fact that medically indicated was broadly defined in the protocol and included patients with cardiopulmonary deterioration, neurological deterioration with concern for the patient’s ability to predict the airway and those with inadequate pain control or agitation. In retrospect, separating these indications for intubation may have helped to better clarify which group(s) of patients had worse outcomes related to the underlying medical condition rather than some possible effect from GA. It is known that some centers perform GA as medically indicated in patients with aphasia or who are unable to follow commands. In IMS III, this approach is suggested by the higher proportion of left hemispheric strokes in the GA group as a whole (Table 1). This practice at some centers may explain in part the relatively higher NIHSS in that group because the NIHSS is biased toward higher scores in dominant hemisphere strokes. The differences could also be accounted for in the lower proportion of patients with angiographic occlusion in the LA group but the on-treatment analysis was not different.

In addition to hemodynamic perturbations, GA may affect outcomes by masking neurological deterioration or headache during the EVT procedure, which could lead to an adjustment of the endovascular approach and avoidance of a major complication, such as vessel perforation. A contrary point of view is that GA may be safer by preventing patient movement which could lead to wire perforation of one of the cerebral vessels. Our theory that there would be a difference in the primary safety measures of sICH and SAH has not been corroborated by the findings. This is in keeping with the findings from other studies that the risk of sICH was the same or lower in the LA group. Therefore, there is to date no evidence that GA is safer than LA. In addition, GA has been associated with significantly higher treatment costs. In a preplanned analysis of costs in the IMS III trial, the average cost of EVT with GA was $46,444 compared with a cost of $30,350 for EVT with LA.

With the rapid rise of retrievable stents as the new standard of interventional care, the applicability of our results to patients treated with such devices is unclear because a minority (n=7) of patients in IMS III was treated with retrievable stents. However, a recent retrospective series of patients treated only with Solitaire FR (Covidien Inc, Irvine, CA) and analyzed for the effect of anesthesia found a significant negative effect of GA compared with LA. In that study, the OR for good outcome was 1.3 (1.01–1.6), P=0.04 in favor of LA when adjusted for anterior circulation strokes and electrively intubated patients only. The OR for mortality with GA was 3.3 (1.6–7.1, P=0.001). This study was a follow-up to the earlier study examining the effect of GA by Abou-Chebl et al and both data sets were garnered from essentially the same centers and operators with the major difference being the use of retrievable stents in the latter study. This suggests
that the effect of GA may be independent of the type of devices used. Further substantiating this assumption is that an analysis of the recent Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial, which was comparable with IMS III but included use of retrievable stents in 97% of endovascular patients, also showed that there was an association with better outcomes (mRS≤2) in patients treated with LA (OR, 2.79 (1.70–4.59; Berkhemer OA, Impact of General Anesthesia On Treatment Effect in the MR CLEAN Trial, Oral Presentation, ISC, February 13, 2015, Nashville, TN).²⁴ Importantly, the 3 recent trials of endovascular thrombectomy where GA was rarely used (9% in Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times [ESCAPE]) provide empirical evidence that the procedure can be safely performed under LA a large majority of the time.²⁵

Surprisingly, GA was not associated with significantly longer treatment times.²⁶ One possible explanation is that when all aspects of EVT preparation are relatively slow, the impact of GA is not perceptible. As these processes become more efficient, the time needed for induction of GA may become increasingly important. However, we did not adjust for case complexity, time of day, etc, factors which could prolong the measured time to groin puncture. These data suggest that in IMS III the observed negative association with GA was unlikely to have been purely because of a delay in treatment.

A final important finding of this study is that compared with intravenous thrombolysis only patients, those receiving EVT without GA had lower in-hospital mortality. Also the medically indicated GA cohort, although small, had significantly worse outcomes and higher mortality compared with the intravenous thrombolysis patients. In combination with other subgroup analyses such as the cohort of patients who had computerized tomographic angiography proven occlusion, these findings may help in the design and patient selection for future trials of EVT: for example, future trials may exclude patients likely to need GA for EVT, increasing their power to detect a benefit.

This study has several limitations. First, not all data were available in all patients. Second, although there was a distinction in reasons for intubation, the definition of medically indicated was not prespecified and could have been open to interpretation as discussed above. Furthermore, we did not collect information on the exact timing of the intubation for GA. If a substantial number of patients were intubated postoperatively for a complication within 7 hours of stroke onset, the results would have been heavily biased against the use of GA. Although anecdotal and post hoc, discussions with the investigators at the highest enrolling centers suggest that the overwhelming majority of patients were intubated preprocedure. The study may have been underpowered to detect a statistically significant difference between routine GA and LA. Finally, BP data during the induction of anesthesia and the EVT procedure were not collected.

In conclusion, in IMS III, GA use in the EVT arm was associated with worse neurological outcomes and increased mortality. The worst outcomes were in the patients with medically indicated GA, although there was a trend for worse outcomes in those patients treated with GA as part of routine care compared with LA. GA was not safer than LA in terms of hemorrhage risk. Finally, GA was not associated with a significant delay in treatment. This is the first prospective study to evaluate a technical aspect of EVT and its effect on outcomes and strongly supports the standardization of EVT procedural details in future trials. These data do not address the potential mechanisms of the GA effect but confirm that there is an effect that should be studied in a prospective, randomized trial. Based on these data, the only data from a prospective study, LA is a viable, safe, and cost-effective option for periprocedural patient management in patients without a clear medical indication for intubation.

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