North American SOLITAIRE Stent-Retriever Acute Stroke Registry

Choice of Anesthesia and Outcomes

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Background and Purpose—Previous work that predated the availability of the safer stent-retriever devices has suggested that general anesthesia (GA) may have a negative impact on outcomes in patients with acute ischemic stroke undergoing endovascular therapy.

Methods—We reviewed demographic, clinical, procedural (GA versus local anesthesia [LA], etc), and site-adjudicated angiographic and clinical outcomes data from consecutive patients treated with the Solitaire FR device in the investigator-initiated North American SOLITAIRE Stent-Retriever Acute Stroke (NASA) Registry. The primary outcomes were 90-day modified Rankin Scale, mortality, and symptomatic intracranial hemorrhage.

Results—A total of 281 patients from 18 centers were enrolled. GA was used in 69.8% (196/281) of patients. Baseline demographic and procedural factors were comparable between the LA and GA groups, except the former demonstrated longer time-to-groin puncture (395.4±254 versus 337.4±208 min; P=0.04), lower National Institutes of Health Stroke Scale (NIHSS; 16.2±5.8 versus 18.8±6.9; P=0.002), lower balloon-guide catheter usage (22.4% versus 49.2%; P=0.0001), and longer fluoroscopy times (39.5±33 versus 28±22.8 min; P=0.008). Recanalization (thrombolysis in cerebral infarction ≥2b; 72.9% versus 73.6%; P=0.9) and rate of symptomatic intracranial hemorrhage (7.1% versus 11.2%; P=0.4) were similar but modified Rankin Scale ≤2 was achieved in more LA patients, 52.6% versus 35.6% (odds ratio, 1.4 [1.1–1.8]; P=0.01). In multivariate analysis, hypertension, NIHSS, unsuccessful revascularization, and GA use (odds ratio, 3.3 [1.6–7.1]; P=0.001) were associated with death. When only anterior circulation and elective GA patients were included, there was a persistent difference in good outcomes in favor of LA patients (50.7% versus 35.5%; odds ratio, 1.3 [1.01–1.6]; P=0.04).

Conclusions—The NASA Registry has demonstrated that clinical outcomes and survival are significantly better in patients treated with LA, without increased symptomatic intracranial hemorrhage risk. Future trials should prospectively evaluate the effect of GA on outcomes. (Stroke. 2014;45:1396-1401.)

Key Words: anesthesia  stroke
During the past 15 to 20 years, endovascular acute ischemic stroke (AIS) treatment has evolved from a primarily pharmaco logically based approach using fibrinolytics to mechanical embolectomy and, most recently, the use of the stent-retrievers.1–4 Although these promising tools have steadily and greatly increased recanalization efficacy, improvement in clinical outcomes, unfortunately, has not kept pace. Of the many probable reasons for this disconnect, many of which are actively being researched (eg, patient selection), periprocedural management has received little scrutiny for its potential role in affecting clinical outcomes. Factors such as blood pressure, fluid, glucose, and temperature management are all linked with stroke outcomes.5 More recently, the issue of procedural anesthesia selection has been raised, which may potentially affect outcomes. Traditionally, intra-arterial therapy (IAT) has been performed under general anesthesia (GA) for patient safety, but recent data have suggested the contrary. Data from a large multicenter retrospective study of 980 patients and a retrospective analysis of 75 patients from the Interventional Management of Stroke II (IMS II) study showed that patients treated with lesser degrees of anesthesia fared better with improved neurological outcomes and lower mortality.6,7 The exact reasons for the apparent detrimental effects of anesthesia are not known but could include hemodynamic perturbations, neurotoxicity, or delays in recanalization treatment.8 One other possible contributor is that GA may mask neurological deterioration because of vascular injury by endovascular devices, the first generations of which are known to be stiffer and more difficult to use than the newer stent-retriever devices.

The North American SOLITAIRE Stent-Retriever Acute Stroke (NASA) Registry was a retrospective registry of multiple high-volume centers performing IAT with the Solitaire FR (eV3 Neurovascular, Irvine, CA) device.9 This device has been associated with rapid recanalization and low rates of intracranial hemorrhage (ICH) compared with the Merci Retriever (Stryker Neurovascular Inc, Fremont, CA) raising the possibility that its use may attenuate the apparent deleterious effects of GA.10 In this study, data on anesthesia modality were reviewed to determine whether use of the Solitaire FR device was also associated with worse outcomes in patients treated under GA.

Methods

The investigator-initiated, retrospective NASA Registry recruited clinical sites within North America to submit demographic, clinical presentation, procedural details, and site-adjudicated angiographic and clinical outcome data on patients with consecutive AIS treated with the Solitaire FR device. Local institutional review board approval was obtained for the data collection. The primary angiographic outcomes were achieving a thrombolysis in myocardial infarction ≥2 or thrombolysis in cerebral infarction ≥2a revascularization. Clinical outcomes were modified Rankin Scale at 90 days, mortality, and symptomatic ICH (sICH). sICH was defined as any parenchymal hematoma, subarachnoid hemorrhage, or intraventricular hemorrhage noted on the initial post-IAT imaging study associated with neurological deterioration within the first 24 hours.

Of the 24 sites, 18 reported data regarding anesthesia use and only patients from these centers were included in this substudy. Periprocedural anesthesia was defined as GA if the patient underwent endovascular intubation along with induction of a deep state of unconsciousness with or without pharmacologically induced paralysis at any time before the end of the IAT procedure. All other patients were defined as undergoing local anesthesia (LA) only, regardless of whether or not they received conscious sedation as long as they were not endotracheally intubated. The indication for anesthesia was defined as routine if it was the standard practice to induce GA in all patients undergoing IAT. Emergent GA was defined as any indication (ie, clinically needed) other than routine practice. Patients arriving from outside hospitals already intubated were labeled as emergent. The criteria for intubation were not defined by the protocol and were defined as per the usual practice and standards at each facility.

All interventional procedures and patient selection were performed according to local standards and protocols. Adjudication of clinical events and outcomes was also performed locally according to site standards and protocols, except that all outcome data collected into the database were defined as described above. This study was performed without industry sponsorship or funding.

Statistical Analysis

The data were housed and analyzed by the central coordinating site, the Medical College of Wisconsin. Descriptive, univariate, and multivariate statistics were performed using JMP 10 software (SAS Institute, Cary, NC). Univariate analysis was performed using the Student t test for continuous variables and χ² or Fisher exact test (for small cell size) for binary variables. The multivariate logistic regression analysis included imbalanced baseline variables and known factors to be associated with poor outcome such as age, National Institutes of Health Stroke Scale (NIHSS), revascularization, and time from onset, and the model was tested using the log likelihood ratio and lack of fit χ² test. An additional analysis restricted to the anterior circulation and electively intubated patients was performed to exclude posterior circulation and emergent intubation confounders.

Results

A total of 354 patients from 24 centers were enrolled in the NASA Registry, but only 18 centers reported on anesthesia resulting in a total of 281 patients enrolled in this study. GA was used in 69.8% (196/281) of patients. Baseline demographics were comparable between the LA and GA groups, except that the LA cohort tended to have a lower mean NIHSS score (16.4±5.8 versus 18.9±6.9, P=0.002; Table 1). A trend for higher initial systolic blood pressures was present in the LA group (P=0.1). Occlusion location and IV tissue-type plasminogen activator treatment were comparable among the cohorts.

Procedural factors are listed in Table 2. Significantly longer mean onset to groin puncture (395.4±254.1 versus 337.4±207.5 min; P=0.04) and mean fluoroscopy times (39.5±33 versus 28±22.8 min; P=0.008) were present in the LA group, although total procedure times were similar (105.7±77 versus 100.6±62 min; P=0.6). Data on door to groin puncture were only available in 80.8% of patients (80.2% LA and 81.1% GA, P=not significant), and when analyzed there was no difference between the groups: mean door to groin time was 141.4±91.4 min in the LA group and 142.2±91.1 min in the GA group (P=0.96). There was a marked difference in the use of a balloon guide catheters in the LA group (22.4% versus 49.2%; P=0.0001) and a slightly lower number of cases requiring ≥3 device passes (13.1% versus 28.1%; P=0.03). There was no difference in the use of IA thrombolysis or in the time to revascularization.

Recanalization success (thrombolysis in cerebral infarction ≥2b [72.94% versus 73.6%; P=0.9] or thrombolysis in myocardial infarction ≥2 [89.3 versus 83.3%; P=0.3]) and the rate
of sICH (7.1% versus 11.2%, \(P=0.4\)) were similar between the LA and GA patients, respectively (Table 2). However, there was a significant difference in the probability of achieving a 90-day good neurological outcome (modified Rankin Scale \(\leq 2\), data available for 252/281[89.7%]) in the LA (52.6%) versus GA (35.6%) patients (odds ratio [OR] 1.4[1.1–1.8]; \(P=0.01\)). In the univariate analysis, there was a trend toward lower mortality in the LA group (23.1% versus 34%, OR 1.4[0.9–2.3]; \(P=0.1\)). In a multivariate analysis, hypertension, NIHSS, unsuccessful revascularization, nonutilization of balloon guide catheter, and GA (OR 3.3[1.6–7.1]; \(P=0.001\)) were associated with mortality (Table 3).

The analysis was also performed with exclusion of the posterior circulation patients (N=27) and patients who were intubated for emergency reasons (Tables 2 and 3) (to remove possible confounders with airway protection and medical comorbidities that necessitate intubation), which left only patients who were treated with GA based on operator preference (N=213). There was a persistent difference in good outcomes in favor of the LA patients (50.7% versus 35.5%, unadjusted OR 1.3[1.01–1.6]; \(P=0.04\)).

**Discussion**

In the NASA Registry of patients with AIS treated with the Solitaire FR device, the use of GA was associated with worse neurological outcomes and increased mortality. The differences were clinically significant with a 40% higher probability of a good clinical outcome in those treated without GA and a 3-fold lower risk of death. Importantly, there was no increased risk of ICH. These data are consistent with recent series, which demonstrated a detrimental effect when GA was used in patients with AIS undergoing IAT.6,7,10

The largest of these was a multicenter retrospective study of 980 patients undergoing IAT, 44% of whom were treated under GA,6 which showed that use of GA was associated with 2.33 OR (95% confidence interval [1.63–3.44]; \(P<0.0001\)) of poor outcome at 90 days and an OR of death of 1.68 (95% confidence intervals [1.23–2.30]; \(P<0.0001\)). As in the NASA Registry, there was no increase in sICH.9

The reason(s) for the differential effects of LA versus GA are not known. There are theoretical concerns of neurotoxicity of certain anesthetic agents, but other agents may be neuroprotective, and specific data on the type of anesthetic used in the GA patients in this study are unavailable.11 More likely is that the induction of GA leads to a reduction in BP, which may be associated with worse outcomes in AIS.12 In their retrospective single center study of 96 patients undergoing IAT, Davis et al13 found an association between GA use and poor outcomes (15% probability of good outcomes versus 60% in the LA patients). The investigators also found an association of good outcomes with SBP >140 mmHg, the presence of which was negatively correlated with GA use (\(r=-0.7\), \(P=0.001\)). Therefore, Davis et al13 postulated that the effects of GA could have been purely because of the changes

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<th>Table 1. Baseline Demographics and Clinical Characteristics</th>
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<td>Age, y</td>
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<td>Race (W/B/O)</td>
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<td>Intravenous r-PA</td>
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<td>Occlusion location M1/ICA/BA</td>
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B indicates black; BA, basilar artery; BP, blood pressure; ICA, internal carotid artery; M1, middle cerebral artery trunk; NIHSS, National Institutes of Health Stroke Scale; O, other; r-PA, recombinant tissue-type plasminogen activator; and W, white.

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<th>Table 2. Angiographic and Clinical Outcomes</th>
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<td>Mean onset-to-groin puncture, min</td>
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<td>Mean fluoroscopy time, min</td>
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<td>Intra-arterial r-PA</td>
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<td>A. Circ only (225/252)</td>
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<td>A. Circ. &amp; elective GA only (213/236)</td>
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<tr>
<td>sICH</td>
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<td>Death</td>
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A. Circ indicates anterior circulation; CI, confidence interval; elective GA, nonemergency general anesthesia; mRS, modified Rankin Scale; OR, odds ratio; sICH, symptomatic intracerebral hemorrhage; r-PA, recombinant tissue-type plasminogen activator; TICI, thrombolysis in cerebral infarction; and TIMI, thrombolysis in myocardial infarction.
was worse than either alone.16 Finally at the lower limit of the combination of arterial obstruction and venous obstruction cerebral venous pressure, which has been noted to occur with cerebral blood flow to the ischemic penumbra potentiating outcomes is unclear but a likely mechanism is a reduction in cerebral autoregulatory curve, animal studies have noted that during anesthesia there is a cycling of cerebral blood flow that has been attributed to a competition between vasodilatory and vasoconstrictive forces raising the possibility that the timing of hypotension, if for example it occurs during a low cerebral blood flow state, may potentiate injury.17

The mechanism by which lower BP may lead to worse outcomes is unclear but a likely mechanism is a reduction in cerebral blood flow to the ischemic penumbra potentiating the extent and degree of injury.14 Also the deleterious effects of reduced arterial BP may be potentiated by any increase in cerebral venous pressure, which has been noted to occur with GA and endotracheal intubation.15 In animal models of stroke, vasoconstrictive forces raising the possibility that the timing of hypotension, if for example it occurs during a low cerebral blood flow state, may potentiate injury.17

One commonality between the published series on this subject and data from this current study is that, in general, patients undergoing GA tended to have a slightly higher stroke severity as measured by NIHSS.6,10 Davis et al11 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. We accounted for this possible confounder by controlling for NIHSS and by performing the analysis with only centers that contain information about averted complications; only a procedural BP readings; therefore, additional studies are needed to confirm these assumptions.6,7,10

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One commonality between the published series on this subject and data from this current study is that, in general, patients undergoing GA tended to have a slightly higher stroke severity as measured by NIHSS.6,10 Davis et al11 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. We accounted for this possible confounder by controlling for NIHSS and by performing the analysis with only centers that perform GA in everyone compared with those that do not. The results were essentially unchanged. Furthermore, a 2 to 3 point difference in the NIHSS is unlikely to account for the observed marked difference completely in good outcomes and mortality and does not convincingly exclude a GA effect on outcomes. We also accounted for vessel occlusion, but not thrombus length, and we performed an analysis excluding patients with posterior circulation occlusions who may have been more likely to require intubation for airway protection. The results remained the same with worse outcomes in the GA cohort.

GA prevents neurological assessments during the procedure, and this has been postulated to decrease the ability of the interventionist to detect ongoing or impending complications, such as worsening of ischemia or ICH.6,18 This theory is difficult to study retrospectively because most patient records do not contain minute-by-minute procedural details nor do they contain information about averted complications; only a prospective study specifically designed to assess intraprocedural decision-making could confirm or disprove it. However, in a small series of patients undergoing intracranial stenting under LA, the authors found that their endovascular technique was affected by clinical factors such as patient reported headache or an observation of ischemia.19 Because the use of the Solitaire FR achieves revascularization faster than the older generation of (ie, Merci or Penumbra) embolectomy devices, the hypothesis in this current study was that the use of the Solitaire FR might remove the relative contribution of the loss of neurological assessment to poor outcomes.3 The results did not confirm this hypothesis, suggesting that the effects of GA may not be device dependent. Although the difference was not statistically significant, the incidence of sICH was numerically lower in the LA group.

The only potentially detrimental effect of LA observed in this study was the longer fluoroscopy times in the LA group. This could be explained by the fact that procedures in awake patients may be prolonged because of the need to attend to the needs of the awake and (sometimes) uncooperative patient and to (possibly) repeat angiographic runs because of motion artifact. However, there was not an increase in the number of device passes or total procedure time (time to recanalization)
nor was there any observed negative association with recanalization, making the finding of prolonged fluoroscopy times of dubious clinical significance.

Although there was no difference in the average number of Solitaire passes, there was a larger number requiring ≥3 passes in the GA group. The reasons for this are unclear and could have been because of chance. However, we did not assess the association between the number of passes and recanalization success, which could explain this finding. In awake patients, some operators may have decided on whether or not to perform further passes based on patient status: if the patient was markedly improving, then they may have stopped altogether even if the angiographic outcome was not optimal but more importantly they may not have performed further passes if there was clinical deterioration, both scenarios potentially leading to a lower number of passes. None of the reasons for terminating the intervention were collected; therefore, we can only speculate on these aspects, and future studies should try to determine prospectively why a decision to terminate the procedure is made to try and address some of these questions. There was also an increased use of balloon-guide catheters in the GA group, which has been associated with increased recanalization efficacy as well as improved outcomes. The explanation for this finding is unclear and may be confounded by the retrospective nature of the study and differences in operator preference and experience.

On a related note, it is unclear why there was an apparent delay in time-to-groin access in LA patients compared with that in GA patients, because induction of GA is (relatively) time consuming. The series by Abou-Chebl et al and Jumaa et al also showed an apparent delay in treatment in the LA group. This difference could be attributable to a perception by physicians at non-GA centers that they have more time and, therefore, move slower than GA centers; this was shown to occur with IV thrombolysis, the more time that remains in the time window the longer it takes for patients to be treated. These data do not support the notion that GA induction results in significant treatment delays. However, because the reasons for GA use were not known, selection bias may contribute to these differences. In some centers, GA use is the standard of care in all patients, whereas at other centers, GA is used in selected patients with more severe strokes or is used only in patients with active respiratory or airway issues (as noted by Davis et al). In fact, the reasons for this delay may be the opposite of the problem with delays in initiation of IV thrombolysis; centers may be avoiding GA use in patients who arrive at later time points to minimize door-to-groin puncture times. This highlights one of the limitations of this retrospective study, and future trials must strive to capture all critical time points to better understand the variables affecting outcomes. Yet despite the longer times to treatment, the LA patients had better neurological outcomes, which further emphasizes the importance of studying this subject in more detail because the time to recanalization is a major predictor of good neurological outcomes.

Finally, this study has corroborated the findings from other trials that complication rates and, in particular, sICHs are not higher in patients treated without GA. This had been a major impetus for performing IAT under GA. In fact, in this study, and similar to other studies, the risk of sICH was the same or lower in the LA group. Several limitations are present in this study, in addition to those discussed above. First, not all outcome data were available in all patients, and not all centers collected their data prospectively potentially causing significant heterogeneity in the quality of the data. Second, the operators in this study were also participants in some of the earlier series, which could lead to bias; however, there is almost no risk of duplication of patients because the Solitaire FR device was only made available in the spring of 2012, well past the publication of the earlier series. This is also a potential strength in that the same investigators and institutions were able to replicate their results with GA and LA before and after the use of the Solitaire FR device. Third, and perhaps most importantly, is that the reasons for intubation in every patient were not specifically defined, which raises the possibility that increased medical comorbidities may explain the differences in outcomes. However, the patients were evenly matched in medical comorbidities. Also, the LA patients were slightly older and were treated later, factors that should have been associated with worse outcomes. Additionally, the results were essentially unchanged when the data were analyzed by excluding patients with vertebro-basilar stroke and limiting the analysis to those centers/operators that perform GA routinely in all patients versus those who do not. Another limitation is that all perioperative BP readings were not available, especially any associated with the induction and maintenance of GA. However, because it is likely that BP fluctuations play a critical role in stroke outcomes, if GA is associated with BP changes, then that by itself may be sufficient reason to reconsider its use during IAT. Also, the specific reasons for patients’ poor outcomes, including death, were not available. Although good outcomes may be associated with successful stroke therapy, poor 90-day outcomes may be because of causes other than procedural factors such as recurrent stroke attributable to reocclusion of same artery, delayed ICH, myocardial infarction, etc. Finally, pretreatment factors such as baseline Alberta Stroke Program Early CT Score (ASPECTS) and the prestroke modified Rankin Scale were not available for each cohort potentially limiting the validity of our results.

Conclusions

In conclusion, GA use during mechanical embolectomy with the Solitaire FR device is associated with worse neurological outcomes and increased mortality. In addition, LA is not associated with increased risk of complications particularly sICH. The reasons for this observed detrimental effect of GA on neurological outcomes are unknown, and the association may not be causative but these findings warrant further study in a prospective trial. However, with the evidence mounting that LA is at least as safe as GA, especially with the planned use of Solitaire FR, the routine use of GA should be reconsidered. If GA is needed, a discussion of these issues and close periprocedural collaboration between the neurointerventionist, anesthesiologist, and the neurointensivist is recommended to ensure careful monitoring and regulation of blood pressure.

Disclosures

Drs Zaidat, Gupta, and Nogueira are consultants on the advisory boards of Covidien and Stryker Neurovascular; Dr Malisch is part of
the SOLITAIRE FR With the Intention for Thrombectomy (SWIFT) Study; and Dr Rai is a consultant for Stryker Neurovascular.

References


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