Comparison of Safety and Clinical and Radiographic Outcomes in Endovascular Acute Stroke Therapy for Proximal Middle Cerebral Artery Occlusion With Intubation and General Anesthesia Versus the Nonintubated State

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Background and Purpose—There is considerable heterogeneity in practice patterns between sedation in the intubated state vs nonintubated state during endovascular acute stroke therapy. We sought to compare clinical and radiographic outcomes between these 2 sedation modalities.

Methods—Consecutive patients with acute stroke due to middle cerebral artery–M1 segment occlusion treated with endovascular therapy between January 2006 and July 2009 were identified in our interventional acute stroke database. Level of sedation was determined as intubated (IS) vs nonintubated (NIS) state. Final infarct volumes on follow-up imaging and clinical outcomes at 3 to 6 months were obtained.

Results—A total of 126 patients were included (73 [58%] NIS vs 53 [42%] IS). In IS patients, intensive care unit length of stay was longer (6.5 vs 3.2 days, \( P < 0.0008\)). Intraprocedural complications were lower in NIS patients compared with IS patients (5/73 [6%] vs 8/53 [15%], respectively), but the difference was not significant (\( P = 0.13\)). In univariate and multivariate analyses, NIS was significantly associated with in-hospital mortality (odds ratio = 0.32, \( P = 0.011\)), good clinical outcome (odds ratio = 3.06, \( P = 0.042\)), and final infarct volume (odds ratio = 0.25, \( P = 0.004\)).

Conclusion—In endovascular acute stroke therapy, treatment of patients in NIS appears to be as safe as treatment in IS and may result in more favorable clinical and radiographic outcomes. Our preliminary observations derived from this retrospective study await confirmation from prospective trials. (Stroke. 2010;41:00-00.)

Key Words: intra-arterial therapy ■ stroke ■ sedation ■ intubation ■ general anesthesia

Owing to the mounting evidence that vessel recanalization is a powerful predictor of outcome in acute ischemic stroke, endovascular acute stroke therapy is being used with increasing frequency. Given the severity of neurologic injury and alterations in the sensorium, patients undergoing acute stroke interventions typically do not cooperate with the procedure. Therefore, conscious sedation or general anesthesia with intubation is typically required in these circumstances. Though important to the eventual procedural outcome, no data regarding intraprocedural sedation or airway management are available for any of the endovascular stroke therapy trials conducted to date. Each method has advantages and disadvantages. Conscious sedation is not prone to the time delays necessary for intubation and ventilation that may translate into considerable delays in time to recanalization. Another advantage of conscious sedation is the ability to perform neurologic assessments at different stages during the procedure. In addition, given that extubation of patients with severe neurologic deficit may only be possible days beyond the actual intervention, performing the procedure in the nonintubated state (NIS) may lead to shorter intensive care unit (ICU) stays, which may facilitate earlier mobilization. Withdrawal of care, a significant cause of mortality in patients with large strokes, is more likely to occur in intubated patients. It is therefore not surprising that intubation was found to be associated with mortality rates as high as 60% to 65% in patients with acute stroke.
Other disadvantages of intubation include preintubation hypotension with administration of induction agents, and uncontrolled hypertension with laryngoscopy and intubation. On the other hand, with conscious sedation, there are concerns related to airway protection and patient discomfort and lack of cooperation, resulting in uncontrolled movements during the procedure. This last aspect represents the main reason for the use of general anesthesia, as it is perceived to be less prone to intraprocedural complications.

Treatment protocols at our center initially included general anesthesia as the standard modality of sedation. However, owing to the theoretical advantages of conscious sedation outlined in the preceding paragraphs, in May 2007 we changed our standard protocols of sedation for acute stroke intra-arterial treatment from preprocedural intubation and general anesthesia to conscious sedation without intubation when feasible. This change in treatment protocols made possible a comparison between the two sedation modalities with regard to procedural safety, as well as clinical and radiographic outcomes. Most cases before that period were performed while patients were in the intubated state (IS), whereas most cases after that time were done while patients were in the NIS.

Because patients with basilar artery occlusion usually present with alteration in level of consciousness, most of those patients treated at our center were referred for intervention in the IS, which limits our ability to make any meaningful comparisons between these two methods of sedation in posterior circulation strokes. Therefore, we limited our analysis to anterior circulation strokes only.

Patients and Methods

This retrospective study was conducted with institutional review board approval. To analyze a homogeneous group of patients with regard to vascular occlusion site, especially because of imbalances in the incidence of occlusion sites between the IS and NIS groups, which could have biased the results of our study, we included in our analysis only those patients with occlusion of the M1 segment of the middle cerebral artery (MCA). We also sought to provide as much uniformity as possible with regard to treatment modalities. Because the MERCI embolectomy device (Concentric Medical Inc, Mountain View, Calif) with or without low-dose tissue-type plasminogen activator (typically <5 mg) administered before embolectomy is the first-line thrombolytic strategy at our institution, we chose to include patients from the time when this device was available at our center.

A total of 464 consecutive patients were identified in the University of Pittsburgh Medical Center acute stroke database. After excluding 62 patients with vertebrobasilar occlusions, we identified 402 patients with MCA occlusion, or baseline serum glucose levels. This change in treatment protocols made possible a comparison between the two sedation modalities of intra-arterial therapy, presence of tandem occlusion, or baseline serum glucose levels.

clinical outcomes or incidence of complications were found between the 2 operators. Level of sedation was determined as IS or NIS. In the IS group, we included only those patients who were intubated specifically for the procedure without any other reasons for intubation. Final infarct volumes on follow-up imaging (typically 24 to 72 hours after the procedure) were calculated by a stroke neurologist (M.A.J. or S.F.Z.) blinded to clinical data from diffusion-weighted magnetic resonance imaging studies (when available) or noncontrast head computed tomography. Visually detected diffusion-weighted imaging or noncontrast head computed tomography abnormalities were manually segmented by a neurologist using a semiautomated commercially available analysis program (GE volume analysis software); the method of calculation uses a previously validated ABC/2 formula. Final outlines were then manually edited. For each patient, clinical outcomes at 3 to 6 months were obtained while blinded to the method of sedation at the time of follow-up in the outpatient clinic or by phone interview. In addition to in-hospital mortality, the primary clinical end point was favorable functional outcome, defined as a modified Rankin Scale score of ≤2 at 3 to 6 months. We also compared the following outcomes between the two groups: final infarct volume, intraprocedural complications, incidence of pneumonia during the first week (extracted from the medical records and as diagnosed by the critical care team caring for the patient), length of stay in the ICU, and need for tracheostomy. For the end points of favorable clinical outcome, inpatient mortality, and final infarct volume, separate univariate and multivariate logistic-regression analyses were performed with demographic, clinical, and baseline radiologic variables of interest. These included age, sex, side of occlusion, admission National Institutes of Health Stroke Scale (NIHSS) score, time from symptom onset to procedure, preprocedural Alberta Stroke Program Early CT Score (ASPECTS), admission systolic blood pressure, admission serum glucose levels, recanalization scores, treatment modality (intraarterial vs intraarterial approach, intraarterial tissue-type plasminogen activator, mechanical thrombosis, combined pharmacologic and mechanical approaches), and presence of tandem extracranial occlusion in addition to the MCA occlusion. Recanalization status was assessed by Thrombolysis In Myocardial Infarction scores. A Thrombolysis In Myocardial Infarction score of 2 or 3 was considered to represent successful recanalization.

Statistical Analysis

Demographic and baseline characteristics between the IS and NIS groups were compared by the χ² test for categorical variables and the Student r test for continuous variables. Univariate analyses were performed. A stepwise logistic-regression model was used to assess independent predictors of favorable clinical outcome, in-hospital death, and favorable imaging outcome, with a probability value ≤0.2 obtained from univariate analyses as an entry criterion. For the purpose of logistic-regression analysis, final infarct volume was dichotomized into a good radiographic outcome when the final infarct volume was ≤70 cm³ and a poor radiographic outcome when the final infarct volume was >70 cm³. This cutoff was chosen on the basis of recent data suggesting that a diffusion-weighted imaging volume of 70 cm³ differentiates best between favorable and unfavorable outcomes in stroke patients treated with intra-arterial thrombolyis.¹⁹

Results

Table 1 summarizes demographic and baseline characteristics in the two groups. IS patients had a statistically significant higher NIHSS score at baseline (17.6 vs 15.1, P=0.004) with a shorter time from symptoms onset to treatment (418 vs 654 minutes, P=0.04). Patients did not significantly differ with respect to the following characteristics: age, preprocedure ASPECTS, preprocedure systemic thrombolyis, and other modalities of intra-arterial therapy, presence of tandem occlusion, or baseline serum glucose levels.
Two of 73 initially NIS patients (2.7%) required intubation during the procedure: 1 patient became severely agitated and developed emesis and an altered level of consciousness. During the procedure: 1 patient became severely agitated and developed emesis and an altered level of consciousness. Except for 1 IS patient who ventriculostomy catheter. Otherwise, other patients who experienced perforations died. Perforations were encountered in 1 NIS and 3 IS patients. These were all caused by microwire or microcatheter perforation and were managed with reversal of antithrombotic agents, occlusion of the perforated vessel with coils or embolic agents, and in some cases, placement of an external ventricular drainage catheter. Except for 1 IS patient who eventually achieved a modified Rankin Scale score of 3, all other patients who experienced perforations died.

The mean length of stay in the ICU for NIS patients was 3.2 days, versus 6.5 days for IS patients (P=0.0008). The rate of tracheostomy was higher in the IS group (7.5% vs 1.4%), with a trend toward significance (P=0.08). The incidence of early (within 7 days) pneumonia was significantly higher in the IS group (30% vs 13.7%, P=0.024).

Clinical and radiographic outcomes were significantly different between the 2 groups, with more favorable outcomes noted in the NIS group. These findings are summarized in Table 2. No significant differences in clinical and radiographic outcomes were observed between different treatment modalities. Clinical outcomes at 3 months were available for 124 of 126 patients, with 2 patients lost to follow-up. A favorable clinical outcome was noted in 47 of 124 (38%) patients and was significantly associated with the NIS in univariate analysis (odds ratio [OR]=3.14, P=0.004). Other variables associated with favorable clinical outcome were age, NIHSS score, successful recanalization, admission glucose value, first systolic blood pressure, and side of stroke, as summarized in Table 3. In multivariable analysis, age (OR=0.92, P<0.001), admission NIHSS score (OR=0.88, P=0.036), successful recanalization (OR=8.6, P=0.015), and conscious sedation (OR=3.06, P=0.042) were found to be independently associated with favorable outcome.

Thirty-nine patients (31%) died during hospitalization. In univariate analysis, conscious sedation without intubation (OR=0.38, P=0.016), in addition to younger age, successful recanalization, and low initial systolic blood pressure, was significantly associated with in-hospital mortality. In multivariable analysis, age (OR=1.04, P=0.040) and conscious sedation (OR=0.32, P=0.011) remained significantly associated with mortality.

The median infarct volume calculated in this series was 65 cm³, with a mean of 10.3 cm³ (SD=115.2). In univariate analysis, conscious sedation was inversely associated with unfavorable radiographic outcome (large infarct volume; OR=0.27, P<0.001). Other variables found to be significantly associated with unfavorable radiographic outcome were initial NIHSS score, unsuccessful recanalization, initial systolic blood pressure, and preprocedure ASPECTS. In multivariable analysis, the inverse association between conscious sedation and unfavorable outcome remained significant (OR=0.25, P=0.004). Other variables found to be independently associated with unfavorable radiographic outcomes in multivariable analysis were preprocedure ASPECTS (OR=0.56, P=0.002), Thrombolysis In Myocardial Infarction ≥2 recanalization (OR=0.54, P=0.036), and admission NIHSS score (OR=1.13, P=0.017).

### Discussion

The main finding of this study is that endovascular therapy for acute ischemic stroke is as safe as in IS patients. In this homogeneous cohort of patients with MCA-M1 segment occlusion treated with similar treatment modalities and by the same operators, we found a significant difference with regard to good clinical outcome, inpatient mortality, and final infarct volume between conscious sedation in the NIS and general anesthesia in the IS, favoring the
former over the latter. However, these preliminary findings are based on a retrospective study involving a relatively small number of patients and need to be confirmed by larger, prospective studies.

There are several potential reasons behind our findings. According to our general approach to patient selection for such interventions, patients in this study were selected for intra-arterial therapy on the basis of a clinical-infarct or perfusion-infarct mismatch, implying that most of the patients had significant amounts of penumbra at the time of their referral for intra-arterial therapy. Because the ischemic penumbra tends to diminish at the expense of ischemic core expansion in a time-dependent process, the time required from decision to intervene to recanalization may have been significantly delayed by intubation and transport of patients in the IS from the emergency department to the angiography suite. Another factor that may explain our findings was the significant variation in blood pressure during induction of anesthesia, especially hypotension, resulting in a more rapid incorporation of the penumbra into the core. The ischemic penumbra has been shown to be vulnerable to variations in blood pressure, as is known to occur during anesthesia induction, thus further compromising flow in the ischemic vascular bed. This effect on local cerebral blood flow was also seen with acute hypocapnia during MCA occlusion in isoflurane-anesthetized rats. Because cerebral steal physiology can occur during intra-arterial therapy, periodic monitoring of Pco2 during intervention might be beneficial. Data on time from decision to intervene to groin puncture, blood pressure variation during the procedure, or intraprocedural Pco2 values were not collected prospectively in our database, and we did not believe that they could be obtained retrospectively in a reliable manner. Therefore, we did not include these variables in our analyses to verify the aforementioned suppositions. However, such data should be recorded in future prospective studies comparing these 2 different methods of sedation in acute stroke interventions.

Central nervous system effects of medications used for general anesthesia versus conscious sedation may have an impact on procedural outcomes. Drugs with relatively brief context-sensitive half-lives, such as propofol and remifentanil, have the potential to decrease the postoperative influence on mental status and level of consciousness. Dexmedetomidine has recently been introduced into clinical practice as an adjunct to sedation and anesthesia, but further experience and evaluation are needed, especially with regard to potential confounding of the neurologic examination. In our study, conscious sedation was achieved with 1 or more of the following agents: ketamine, propofol, fentanyl, Midazolam, and most recently, dexmetatomidine.

The primary reason for using general anesthesia in our center in the past was to minimize motion artifact and to perform the procedure in a controlled and safe environment. A major reason of concern, that of a higher likelihood of intraprocedural complications, especially perforations, was the main factor leading to performance of these procedures on patients in the IS. This concern was not substantiated by the results of our current study, as we did not see a higher incidence of intraprocedural complications in patients in the awake state. Unexpectedly, a higher incidence of perforations was seen in IS patients. Although we believe that this last observation may be due to chance, our findings indicate that from the standpoint of complications, endovascular treatment of ischemic stroke is as safe in the awake state as in the IS.

Another detrimental aspect related to intubation found in our study was prolonged ICU stay and higher rates of tracheostomy in IS patients. This is most likely related to difficulties associated with weaning patients off the ventilator after the procedure, given their compromised neurologic status and inability to protect their airway. It should be noted that although intubation is oftentimes performed with the specific purpose of protecting the airway and preventing

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**Table 3. Univariate Analyses: Significant Predictors of Favorable Clinical Outcome (Modified Rankin Scale Score <2), In-Hospital Mortality, and Final Infarct Volume**

<table>
<thead>
<tr>
<th></th>
<th>Modified Rankin Scale Score ≤2</th>
<th>In-Hospital Mortality</th>
<th>Infarct Volume &gt;70 cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>P Value</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>0.94</td>
<td>&lt;0.001</td>
<td>0.91–0.97</td>
</tr>
<tr>
<td>Female</td>
<td>0.49</td>
<td>0.056</td>
<td>0.24–1.02</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>0.87</td>
<td>0.001</td>
<td>0.80–0.94</td>
</tr>
<tr>
<td>Tandem occlusion</td>
<td>1.64</td>
<td>0.27</td>
<td>0.68–3.92</td>
</tr>
<tr>
<td>TIMI recanalization ≥2</td>
<td>4.52</td>
<td>0.009</td>
<td>1.51–49.35</td>
</tr>
<tr>
<td>Conscious sedation</td>
<td>3.14</td>
<td>0.004</td>
<td>1.04–9.01</td>
</tr>
<tr>
<td>Time to procedure</td>
<td>1.00</td>
<td>0.26</td>
<td>0.99–1.00</td>
</tr>
<tr>
<td>Admission glucose</td>
<td>0.99</td>
<td>0.017</td>
<td>0.98–1.00</td>
</tr>
<tr>
<td>First systolic blood pressure</td>
<td>0.98</td>
<td>0.023</td>
<td>0.96–0.99</td>
</tr>
<tr>
<td>Side (left)</td>
<td>0.45</td>
<td>0.037</td>
<td>0.08–0.80</td>
</tr>
<tr>
<td>ASPECTS</td>
<td>1.46</td>
<td>0.082</td>
<td>0.95–2.26</td>
</tr>
</tbody>
</table>

TIMI indicates Thrombolysis In Myocardial Infarction.
aspiration pneumonia, our data suggest that this complication occurs more frequently in the IS than in the NIS. Because this may be related to difficulties encountered when attempting to wean patients off the ventilator and the occurrence of ventilator-associated pneumonia, in those instances in which intubation is considered unavoidable it may therefore be beneficial to attempt extubation as soon as possible after the procedure to avoid complications related to prolonged ICU stay.

Despite the fact that these procedures were performed while the patient was under conscious sedation, our procedures were performed in the presence of an anesthesiologist who provided management of sedation, blood pressure, and untoward procedural events. One common potential problem in NIS cases is oversedation, which can result in upper-airway obstruction and compromised gas exchange. Evaluation for airway protection in an emergency situation should take into account that direct access to the airway may be limited by table or room logistics. In our study, as a consequence of oversedation or worsening of cerebral ischemic damage with resultant obtundation and/or emesis, a small proportion of patients required intubation during the procedure. It is therefore recommended that acute stroke interventions, even when performed on patients in the awake state, should be carried out in the presence of or with immediate availability of experienced anesthesia or critical care trained providers who can rapidly manage untoward events, including securing the airway.

Our study has several limitations, mainly derived from its retrospective design. It is important to mention the difference in baseline stroke severity (NIHSS score). We consider this to be a significant confounder of our analysis. However, the differences in baseline stroke severity were relatively small. Moreover, when correcting for this imbalance in the multivariate analysis, the positive association between clinical outcome, mortality, and infarct volume did not lose its significance. Another potential limitation is evolving operator experience and technological advances related to mechanical embolectomy devices, given that conscious sedation was implemented later during the time period included in this study. Given the nonsignificant difference in recanalization rates between the 2 groups (see Table 1), it is unlikely that this factor influenced our results in a significant way.

Given the limitations of this retrospective study involving a relatively small sample size, we do not view our results as definitive proof that performing stroke interventions on patients in the NIS is superior to the use of general anesthesia. Rather, we regard these preliminary data as hypothesis generating and also as a source of reassurance for those practitioners who perform these procedures in NIS that this approach to acute stroke intervention is not inferior compared to IS.

Disclosures
Dr Jovin is a consultant for Ev3, Inc, Concentric Med, Inc, and Co-Axia, Inc. Dr Horowitz is a consultant for Ev3, Inc. There are no other conflicts to report.

References
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Stroke. published online April 29, 2010;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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