Type of Anesthesia and Differences in Clinical Outcome After Intra-Arterial Treatment for Ischemic Stroke

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Background and Purpose—Intra-arterial treatment (IAT) in patients with acute ischemic stroke (AIS) can be performed with or without general anesthesia (GA). Previous studies suggested that IAT without the use of GA (non-GA) is associated with better clinical outcome. Nevertheless, no consensus exists about the anesthetic management during IAT of AIS patients. This study investigates the association between type of anesthesia and clinical outcome in a large cohort of patients with AIS treated with IAT.

Methods—All consecutive patients with AIS of the anterior circulation who received IAT between 2002 and 2013 in 16 Dutch hospitals were included in the study. Primary outcome was functional outcome on the modified Rankin Scale at discharge. Difference in primary outcome between GA and non-GA was estimated using multiple ordinal regression analysis, adjusting for age, stroke severity, occlusion of the internal carotid artery terminus, previous stroke, atrial fibrillation, and diabetes mellitus.

Results—Three hundred forty-eight patients were included in the analysis; 70 patients did not receive GA. Non-GA was significantly associated with good clinical outcome (odds ratio 2.1, 95% confidence interval 1.02–4.31). After adjusting for prespecified prognostic factors, the point estimate remained similar; statistical significance, however, was lost (odds ratio 1.9, 95% confidence interval 0.89–4.24).

Conclusions—Our study suggests that patients with AIS of the anterior circulation undergoing IAT without GA have a higher probability of good clinical outcome compared with patients treated with general anesthesia. (Stroke. 2015;46:1257-1262. DOI: 10.1161/STROKEAHA.115.008699.)

Key Words: acute stroke ■ anesthesia ■ conscious sedation ■ thrombectomy ■ thrombolytic therapy
Currently, no consensus exists about the optimal anesthetic management of AIS patients during IAT. Previous studies had several methodological limitations that prevent to draw definite conclusions. Most important was the imbalance in stroke severity at baseline in most studies, resulting in more severe strokes in the GA group as compared with the non-GA group. Furthermore, the majority of studies had small numbers of patients. In the absence of definite evidence, current practice is largely based on local protocols and preferences of the neurointerventionalists. Possible advantages of GA are (1) immobilization of the patient to prevent wire-induced vessel injury and to facilitate navigation with a quicker recanalization; (2) adequate ventilation and airway protection; and (3) limiting patient discomfort. On the other hand, a non-GA approach (1) may reduce time to treatment initiation; (2) allows neurological assessments during and after the procedure; (3) does not induce blood pressure lowering; and (4) does not require intubation. Nonetheless, when using a non-GA approach, there is a chance of a need to convert acutely to GA accompanied by emergency intubation, which is associated with a higher rate of aspiration pneumonia and poor outcome.

In this retrospective study among 16 Dutch hospitals, we aimed to evaluate the relation between anesthetic management during IAT and clinical outcome. In most intervention centers in the Netherlands, a standard strategy regarding anesthetic management for acute stroke interventions is applied, thereby limiting bias through patient selection by baseline stroke severity in this study. We hypothesized that a non-GA approach during IAT in patients with AIS of the anterior circulation is associated with a better clinical outcome compared with GA based on a potentially shorter time from onset to treatment initiation, avoidance of potentially harmful blood pressure changes, and quicker recovery without the use of GA.

Methods

We conducted a retrospective cohort study in patients from the pretreatment cohort of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands (MR CLEAN), which consists of all consecutive patients with AIS treated with IAT in 16 stroke centers in The Netherlands. Information concerning procedures and treated patients was gathered to assess pretrial experience in centers that were committed to participate in the MR CLEAN trial. The registry started in October 2002 and continued until a center started participation in the trial. The institutional review board from the coordinating institution approved registration and use of the data. We only included patients with an anterior circulation stroke in our analysis. Patients were treated intra-arterially with a thrombolytic agent, a dedicated clot retriever or a retrievable stent. The method of IAT was left to the discretion of the treating neurointerventionalists.

Study Procedures

All centers kept a prospective registry of patients who received IAT. Data collection itself was largely retrospective. Demographic variables, premorbid stroke risk factors, National Institutes of Health Stroke Scale (NIHSS) score at baseline, use of intravenous tissue-type plasminogen activator, timing of baseline and treatment procedures, treatment type (intra-arterial thrombolytics, mechanical treatment, or both), and type of anesthesia (GA or non-GA) were obtained from medical charts and intervention reports by trained medical researchers. When necessary and possible, NIHSS at baseline was reconstructed from clinical data with a modified algorithm. When missing, IAT time points were reconstructed using angiogram times: for start of IAT, time of first scan minus 5 minutes; for end of IAT, time of last scan plus 5 minutes.

Outcomes

Modified Rankin Scale (mRS) for functional outcome at discharge was assessed by a certified neurologist or neurology fellow. Good clinical outcome was defined as mRS of ≤2. Grade of recanalization was assessed with the modified Thrombolysis in Cerebral Infarction score (mTICI). Recanalization was defined as mTICI score 2b or 3 on Digital Subtraction Angiography imaging at the end of the procedure. Three experienced observers from a center that was not involved in the treatment assessed all Digital Subtraction Angiography runs. Observers were blinded for baseline data of the patient and for intervention center. All periprocedural and postprocedural complications, including conversion from local to GA, were recorded from intervention and imaging reports and patient records. Symptomatic intracranial hemorrhage (SICH) was defined as parenchymal hemorrhage at any site in the brain on the CT-scan, being compatible with documented neurological deterioration. Asymptomatic intracranial hemorrhage was defined as parenchymal hemorrhage at any site of the brain found on follow-up CT-scan without neurological deterioration.

Statistical Analysis

Analyses were based on the intention to treat principle. Conversions from non-GA to GA were therefore counted in the non-GA arm of the study. Descriptive statistics was expressed as means with standard deviation or medians with interquartile range (IQR). Groups (non-GA versus GA) were compared by the chi-square test for categorical variables and the Student-t test or, in case of a non-normal distribution, the Mann–Whitney U test for continuous variables. Univariable logistic analysis was performed to determine an association between type of anesthesia and good clinical outcome. Multivariable logistic regression analysis was performed to adjust for predefined prognostic variables: age, stroke severity (NIHSS) at baseline, occlusion of the internal carotid artery terminus, history of previous stroke, atrial fibrillation, and diabetes mellitus. Additionally, we performed multivariable ordinal logistic regression analysis to assess the adjusted common odds ratio for a shift in direction of a better outcome on the mRS, adjusted for the aforementioned variables. Statistical analyses were performed using SPSS version 22.0.

Results

We identified 369 patients with an anterior circulation stroke and available information on anesthetic management during IAT and functional outcome at discharge. Of these 369 patients, we excluded 21 patients for multiple reasons, for example, patients already under GA for other procedures, lack of information on timing of procedures, or cross-over to no IAT (see online-only Data Supplement for patient flow-chart). Three hundred forty-eight patients were used for the analysis; 278 patients were treated without GA and 70 patients with GA. Information on the use of CS and specific agents were not available in most of the cases. Patients received non-GA based on standard strategy in 274 cases. In 4 cases, procedure was started without GA, despite the local standard strategy indicating GA. The majority of patients (N=63) received GA as initial treatment modality, based on the local standard strategy. Seven patients received GA because of agitation, respiratory insufficiency, or decreased level of consciousness before start of the treatment, whereas they would normally be treated without GA.
Ten patients (10/278 [4%]) in the non-GA group converted to GA during treatment. In 9 patients, reason for conversion was agitation and patient movement. One patient had respiratory insufficiency during treatment initiation. These converted cases were included in the non-GA group based on the intention to treat principle.

Baseline
Patients treated under GA were significantly younger (57 years versus 62 years) and less often had atrial fibrillation (9/70 [29%] versus 40/278 [16%]). Furthermore, patients in the GA group had a longer time from onset of symptoms to start of IAT of 00:20 hours (median 04:01; interquartile range 01:53 hours versus 03:40; interquartile range 01:41) and were more frequently treated with mechanical thrombectomy only (32/70 [46%] versus 61/278 [22%]). The distribution of baseline stroke severity (NIHSS), pretreatment with intravenous tissue-type plasminogen activator, and occlusion site was similar in both groups (Table 1).

Clinical Outcome
A total of 82 (82/348 [24%]) patients were functionally independent (mRS 0–2) at discharge. Good clinical outcome was seen in 26% (72/278) of patients in the non-GA group and in 14% (10/70) of patients in the GA group. A higher mortality rate was seen in the GA group (15/70 [21%]) compared with the non-GA group (46/278 [17%]); however, this difference was not statistically significant (Table 2). The distribution of the mRS in both treatment groups is presented in Figure.

In unadjusted logistic regression analysis, non-GA was significantly associated with good clinical outcome (odds ratio 2.1, 95% confidence interval 1.02–4.31). After adjusting for prespecified prognostic factors, the point estimate remained positive and, however, did not reach statistically significance (odds ratio 1.9, 95% confidence interval 0.89–4.24). The additional multivariable ordinal regression analysis showed a shift in distribution on the mRS in favor of the non-GA group (adjusted common odds ratio 1.6, 95% confidence interval 0.98–2.54). This also was not statistically significant.

Periprocedural Complications
Vessel perforation was seen in 4 patients (4/278 [1%]) treated without GA and did not occur in patients treated under GA. Two of these 4 patients had an accompanying SICH with an outcome of respectively 4 and 5 on the mRS at discharge. From one patient, neither SICH nor asymptomatic intracranial hemorrhage was reported and had an mRS of 3 at discharge, and one patient had an asymptomatic intracranial hemorrhage with mRS 4 at discharge. Dissection of the internal carotid artery during treatment was seen in both groups (non-GA: 12/278 [4%] versus GA: 270 [3%]), as well as device-related complications (non-GA: 6/278 [2%] versus GA: 370 [4%]). These included failure to deploy the retrievable stent, a broken guidewire, a broken stent, and a part of device unable to retrieve.

Postprocedural Complications
Postprocedural complications are summarized in Table 2. There was no difference in occurrence of SICH or asymptomatic intracranial hemorrhage between the 2 treatment groups.

Discussion
Our study suggests that patients with anterior circulation AIS treated with IAT, who did not receive GA, have a higher...
probability of good clinical outcome compared with patients who received GA. Furthermore, we observed that IAT was initiated sooner after symptom onset in patients treated without GA as compared with GA. We did not find major differences with regard to safety parameters between the 2 treatment modalities.

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>No General Anesthesia (n=278)</th>
<th>General Anesthesia (n=70)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0–2, n (%)</td>
<td>72 (25.9)</td>
<td>10 (14.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>46 (16.5)</td>
<td>15 (21.4)</td>
<td>0.34</td>
</tr>
<tr>
<td>mTICI score post treatment*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, n (%)</td>
<td>36 (13.6)</td>
<td>11 (15.7)</td>
<td>0.55</td>
</tr>
<tr>
<td>1, n (%)</td>
<td>19 (7.2)</td>
<td>6 (8.6)</td>
<td>0.62</td>
</tr>
<tr>
<td>2a, n (%)</td>
<td>97 (36.6)</td>
<td>19 (27.1)</td>
<td>0.22</td>
</tr>
<tr>
<td>2b, n (%)</td>
<td>35 (13.2)</td>
<td>14 (20.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>3, n (%)</td>
<td>78 (29.5)</td>
<td>20 (28.6)</td>
<td>0.93</td>
</tr>
<tr>
<td>Full recanalization (TICI 2b/3)</td>
<td>113 (42.6)</td>
<td>34 (48.6)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Procedural complications

| Total complications, n (%) | 50 (18) | 9 (12.9) | 0.31 |
| Vessel perforation, n (%) | 4 (1.4)  | 0 (0)    | 0.31 |
| Dissection, n (%)          | 12 (4.3) | 2 (2.9)  | 0.58 |
| Device-related complications, n (%) | 6 (2.2) | 3 (4.3) | 0.32 |
| Hemodynamic and airway complications, n (%) | 2 (0.7) | 0 (0)   | 0.48 |
| Reperfusion syndrome, n (%) | 1 (0.4) | 0 (0)    | 0.62 |
| Migration of thrombus, microthrombi, or restenosis, n (%) | 10 (3.6) | 4 (5.7) | 0.42 |
| Seizures during treatment, n (%) | 3 (1.1) | 0 (0)    | 0.38 |
| Groin hematoma, n (%)       | 12 (4.3) | 0 (0)    | 0.08 |

Postprocedural complications

| SICH, n (%) | 33 (11.9) | 8 (11.4) | 0.92 |
| AICH, n (%) | 32 (11.5) | 9 (12.9) | 0.76 |
| Progression of stroke†, n (%) | 28 (10.1) | 12 (17.1) | 0.15 |
| Pneumonia, n (%) | 41 (14.7) | 9 (12.9) | 0.69 |
| Other infection, n (%) | 23 (8.3) | 3 (4.3) | 0.26 |
| Cardiac arrhythmias‡, n (%) | 6 (2.2) | 0 (0) | 0.38 |
| Myocardial infarction, n (%) | 1 (0.4) | 0 (0) | 0.62 |
| Decompensated heart failure, n (%) | 2 (0.7) | 1 (1.4) | 0.57 |
| Major extracranial hemorrhage, n (%) | 4 (1.4) | 2 (2.9) | 0.42 |
| PE/DVT, n (%) | 2 (0.7) | 1 (1.4) | 0.57 |
| Seizures, n (%) | 10 (3.6) | 5 (7.1) | 0.19 |

Our findings are consistent with earlier findings in both terms of clinical and safety outcomes between the 2 treatment types. However, previous studies reported an imbalance in baseline NIHSS in favor of non-GA-treated patients, which could have influenced outcome. In contrast, our study had equal scores on baseline NIHSS. Hence, difference in baseline stroke severity is not the reason for improved clinical outcome after non-GA patients in our cohort.

How can we explain improved outcome in patients treated without the use of GA? First of all, it is known that inhaled or intravenous anesthetic agents can alter blood CO2 levels and blood pressure shifts, which can lead to changes in cerebral autoregulation and consequently in decrease of cerebral bloodflow, leading to extension of ischemic injury. Use of propofol and induction dosages of fentanyl predicted postinduction hypotension in a study of Reich and colleagues. Furthermore, some anesthetic gases might act as a vasodilator, resulting in the reverse Robin Hood syndrome, with steal from blood flow of the affected vascular territories toward unaffected territories, further compromising flow in the ischemic area. There are data that support these findings in AIS patients treated with IAT. Davis et al found that lower blood pressures were associated with worse outcomes in patients undergoing CS or GA, and the mean systolic blood pressure in patients undergoing CS was 135 mm Hg compared with 104 mm Hg in patients with GA. Additionally, in a retrospective study of 126 patients with a middle cerebral artery stroke treated with IAT, Jumaa et al showed that final infarct volume was significantly larger in intubated patients versus nonintubated patients (mean infarct volume [cm3] 147 versus 80.2, P=0.002). In our study, we were unable to collect adequate information on type of anesthetic agents, blood pressure, CO2, and cerebral bloodflow during treatment nor final infarct volumes to confirm these data.

Another reason often suggested for the difference in outcome could be a higher rate of aspiration and pneumonia in intubated patients and contribution of pneumonia to poor outcome. However, we found a lower rate of pneumonia in the GA group, and therefore, this phenomenon cannot explain the differences in clinical outcome in our study. Conversely, lack of airway protection by the absence of intubation could lead to higher rates of pulmonary aspiration in non-GA patients. Patients with AIS of large cerebral artery may have a degree of dysphagia and are unlikely to have been fasted before intervention. The urgent need for conversion to GA may occur, accompanied by a higher risk of aspiration. Most previous studies did not examine the rate of conversion from non-GA to GA. In our study, only 10 patients in the non-GA group were converted to GA. No effect on clinical outcome was seen in these patients. The small number of converted patients in our study demonstrates that in current medical practice, the risk of conversion to GA is relatively small, thereby not clearly influencing clinical outcome in the non-GA group.

The most important factor leading to poor outcome could be that GA may lead to treatment delay resulting in a prolonged onset to recanalization time and therefore reduce the chance of good clinical outcome. However, 2 previous studies that investigated this perception found no difference in time to treatment between GA and non-GA and between intubated and...
nonintubated state, respectively.\(^6,7\) In our cohort, IAT in patients treated under GA was started 20 minutes later than in patients treated without GA. Because time from stroke onset to treatment is an important factor for outcome after acute stroke treatment, this may account for difference in clinical outcome. To our knowledge, this is the first study to demonstrate a difference in time to treatment between GA and non-GA. Future studies need to confirm this and should use specific time points to provide insight into the point at which most time is lost.

The main reason for neurointerventionalists to use GA is to minimize patient movement. Awake patients could be agitated during treatment, resulting in head movements that affect Digital Subtraction Angiography images. As a result, longer times to recanalization may occur. Major concern, of course, is increasing risk of procedural complications, such as vessel perforation or dissection and subsequent intracranial hemorrhage. In our group of non-GA patients, rate of vessel perforation was low and SICH was seen as often as in patients treated under GA. Other studies showed similar safety result, indicating that a non-GA approach seems to be a safe choice.

As we know from previous studies, higher recanalization leads to better clinical outcome.\(^2,3\) In a meta-analysis from Brinjikji et al, which included all available studies on anesthesia and IAT of AIS, a significant difference was found in recanalization grades in favor of non-GA.\(^15\) In our study, full recanalization was reached in similar percentages of patients in both treatment groups. So, we can conclude that higher recanalization may not account for better outcomes in the non-GA group in our cohort of patients.

The effect of anesthesia on clinical outcome in AIS patients remains a black box, containing several factors that could influence outcome. Our study did not answer the question which individual parameters are responsible for worse clinical outcome in patients treated under GA. Faster initiation of treatment from stroke onset could be one of the major factors in this study.

**Limitations**

Our study does have several limitations. One of the major limitations is the retrospective and nonrandomized nature. Choice of anesthesia was based on standard local strategy or preference of the neurointerventionalist. The latter could have led to selection bias or confounding by indication or center, although a standard strategy regarding anesthetic management for acute stroke interventions is applied in most centers. Also the majority of centers and operators preferred not to use GA; therefore, group sizes were unequal. Optimal method would include randomization between GA and non-GA. Currently, the ANSTROKE (Sedation Versus General Anesthesia for Endovascular Therapy in Acute Stroke—Impact on Neurological Outcome) trial is randomizing AIS patients between GA and sedation only.\(^23\) Furthermore, mRS scores were only available at discharge. It is preferable to assess the effect of anesthesia on clinical outcome over a longer period of time.

**Conclusions**

Overall, the results of our study are in line with previous studies and show that patients who do not receive GA have a higher probability of good clinical outcome and do not have higher complication rates than patients who undergo GA. Local anesthesia, with the possible use of CS, during IAT for AIS seems a good strategy if possible.

**Appendix**

The MR CLEAN pretrial study group.

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Disclosures
Dr Majoie’s institution received fees for his role as a consultant for Stryker (speakers bureau/lecture fees). Dr Boiten has received honors for his role as a consultant for Boehringer Ingelheim. The other authors report no conflicts.

References
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for the MR CLEAN pretrial study group

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SUPPLEMENTAL MATERIAL

Patient flow-chart

369 IA treated patients with AIS of the anterior circulation

11 patients who received IAT during elective procedure

5 patients who eventually did not receive IAT

4 patients with missing information

1 patient who received thrombectomy for cerebral venous thrombosis

348 patients used for the analysis

IA indicates intra-arterial; AIS, acute ischemic stroke, IAT, intra-arterial treatment
Figure. Ninety-day modified Rankin Scale (mRS) distribution for endovascular therapy vs intravenous tissue-type plasminogen activator in the Interventional Management of Stroke 3 trial stratified by good, intermediate, and poor collateral status as per the 3 collateral scores. Black lines indicate shifts in mRS 0 to 1 and mRS 0 to 2, across treatment types. tPA indicates tissue-type plasminogen activator.
Systolic Blood Pressure and Mortality After Stroke

Too Low, No Go?

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(Stroke. 2015;46:1307-1313.)

Key Words: blood pressure □ hypertension □ mortality □ Nutrition Surveys □ secondary prevention □ stroke

Table 4. Crude and Adjusted Hazard Ratios of All-Cause Mortality or Vascular Mortality by SBP

<table>
<thead>
<tr>
<th>SBP Group</th>
<th>All-Cause Mortality (n=130 Events)</th>
<th>Vascular Mortality (n=61 Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>GA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥140 mmHg</td>
<td>1.05 (1.06–1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤139 mmHg</td>
<td>1.00 (0.66–1.67)</td>
<td>0.834</td>
</tr>
<tr>
<td>Adjustable*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP ≥140 mmHg</td>
<td>1.05 (1.06–1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;120 mmHg</td>
<td>0.86 (0.46–1.67)</td>
<td>0.627</td>
</tr>
<tr>
<td>≤120 mmHg</td>
<td>1.05 (1.06–1.09)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Adjusting for age, sex, race/ethnicity, poverty income ratio, hypertension, total serum cholesterol >200 mg/dL, coronary artery disease, angina, congestive heart failure, body mass index, use of antihypertensive medication(s), smoking.