Analysis of the Safety and Efficacy of Intra-Arterial Thrombolytic Therapy in Ischemic Stroke

Rejane C. Lisboa, MD; Borko D. Jovanovic, PhD; Mark J. Alberts, MD

Background and Purpose—Intra-arterial thrombolytic therapy (IAT) may be a treatment option for patients with ischemic stroke. We analyzed the safety and efficacy of IAT on the basis of published data.

Methods—We searched computerized databases for studies using IAT in ≥10 patients with ischemic stroke. Some studies had control patients for comparison. Data were collected on age, stroke territory, time to treatment, medication, site of arterial occlusion and recanalization on angiogram, outcomes, and symptomatic intracranial hemorrhage (SICH).

Results—The analysis included 27 studies with 852 patients who received IAT and 100 control subjects. There were more favorable outcomes in the IAT than in the control group (41.5% versus 23%, P=0.002), with a lower mortality rate for IAT (IAT, 27.2%; control group, 40%, P=0.004). The IAT group had an odds ratio of 2.4 (95% CI, 1.45 to 3.85) for favorable outcome. SICH was more frequent in the IAT group compared with the control group (9.5% versus 3%, P=0.046). The subgroup of patients receiving a combination of intravenous thrombolytic therapy and IAT had more favorable outcomes than the IAT alone subgroup, but this trend did not reach statistical significance (53.6% versus 41.5%, P=0.1). Among the patients treated with IAT, those who had supratentorial strokes were more likely to have favorable outcomes than those with infratentorial strokes (42.2% versus 25.6%; P=0.001; odds ratio, 2.0; 95% CI, 1.33 to 3.0).

Conclusions—IAT for ischemic stroke appears efficacious but carries an increased risk of SICH. Further prospective studies are needed to prove the safety and efficacy of IAT in stroke. (Stroke. 2002;33:1111–1117.)

Key Words: stroke, ischemic • thrombolytic therapy

Stroke is the third-leading cause of death and a leading cause of adult disability in the United States.1 The first report on an efficacious treatment for acute ischemic stroke (AIS) was published in 1995 by the NINDS rt-PA Stroke Study Group.2 They showed that intravenous recombinant tissue plasminogen activator (rtPA) significantly improved neurological outcome when administered up to 3 hours after symptom onset. Postmarketing studies have shown that intravenous rtPA is beneficial when the NINDS study guidelines are followed.3–5 However, the brief treatment time window of 3 hours significantly limits the number of treatable patients. Studies suggest that only 1% to 2% of ischemic stroke patients receive intravenous rtPA,6–8 although isolated centers may have higher rates of treatment.9,10 Efforts to increase public awareness of stroke and rtPA use will only slowly increase the number of treatable patients. A recent project used community and professional behavioral interventions to improve the delivery of intravenous rtPA therapy for acute stroke. They reported an increase from 2.2% to 8.6% in the number of patients with ischemic stroke treated with intravenous rtPA.11

Intra-arterial thrombolytic therapy (IAT) for AIS may be a treatment option with an expanded treatment time window, as shown by the 6-hour window used in the PROACT II study.12 It could benefit selected patients less likely to respond to intravenous thrombolytic therapy (IVT), such as those with large-vessel occlusions. Recanalization of these vessels by IVT was shown to be uncommon.13 IAT could also be used in patients in the early postoperative period when the systemic effects of IV rtPA are not desirable.14,15 Most studies of IAT were small and did not have randomized control subjects.16 Therefore, conclusive data about its safety and efficacy have not been established.

To address these concerns, we analyzed published studies on IAT for AIS. The goal was to better understand the safety and efficacy of this form of therapy.

Methods

Computerized databases (MEDLINE, PREMEDLINE) were searched for studies using IAT for AIS, including trials of IAT in combination with IVT. Cross-references were also used. Studies with <10 patients or those including patients with transient ischemic attacks were excluded. When patients who were presented in >1 publication were identified, they were counted only once. When patients were allocated or randomized to treatment, we counted only those who actually received IAT. Two randomized studies15,17 and 2 case series18,19 had control groups that we used for statistical comparison.
Data were collected on mean ages, stroke territory (supratentorial or infratentorial), time window to treatment, medication used, site of arterial occlusion and recanalization on angiography, outcomes, and symptomatic intracranial hemorrhage (SICH). Studies were included in the final analyses if they presented comparable information on at least SICH, neurological outcome, and death.

Patients defined in this analysis as having a favorable outcome were those with a modified Rankin Scale score of 0 to 2, a Glasgow Outcome Scale score of 1, or a Barthel Index score >95. When no outcome scale was used, patients were counted as having a favorable outcome when classified by the studies in the following categories: no, mild, minor, or slight neurological deficits; normal; complete or nearly complete symptom resolution; and able to function in society. When a study did not allow separation of the patients into these categories, it was excluded. The outcomes were measured at 90 days in most studies, but some reported earlier or later outcomes.

We defined an intracranial hemorrhage as symptomatic when the authors stated so, alluded to or described clinical deterioration, or characterized the hemorrhage as massive or causing midline shift or when the intracranial hemorrhage was followed by death.

We defined successful recanalization if reported by the authors as present, complete, almost complete, successful, partial, moderate, or >40% recanalization or described by the Thrombolysis in Myocardial Infarction classification as grades 2 to 3. Recanalization was not counted if followed by rethrombosis in the initial few hours.

Any-cause mortality up to 90 days was used for mortality outcomes, although some studies presented only earlier outcomes.

We pooled all data, assuming homogeneity of studies and their results, for an overall analysis. For specific subgroup analyses such as supratentorial and infratentorial strokes, we pooled appropriate studies and patients. For the occurrence of events (favorable outcome, SICH, death), we tested the hypothesis of no difference between groups using log-transformed probabilities. Approximate variances were computed with Taylor expansion. Two-sided alternatives were assumed, and 2-sided probability values <0.05 were considered significant. For continuous variables, we used a t test and variances computed from grouped data. For computation of confidence intervals (CIs) for odds ratios (ORs), we used a log method.

### Results

The final analysis included 27 studies published from 1988 to 2002 with 852 patients in the IAT group and 100 in the control group. Forty-one other studies were excluded. Table 1 lists the 27 studies used in our analysis with the number of patients treated with IAT and the number of control patients. Control patients received heparin (n = 852), aspirin (n = 10), heparin followed by warfarin (n = 8), or aspirin (n = 4).

Most of the studies were case series, either prospective or retrospective. Three were randomized trials, 2 comparing IAT with placebo and 1 comparing combined IVT/IAT with IAT alone. The PROACT II study was the only large, randomized, phase III trial of IAT.

The mean ages were 63.5 years for patients who received IAT (age was not available in 3 studies with a total of 104 patients) and 65.3 years for control subjects, which is not a significant difference (P = 0.8). Treatment medications, doses, and number of patients treated are listed in Table 2. Most treated patients received urokinase, which is not currently available in the United States.

The mean times to begin therapy ranged from 2.7 to 21.1 hours. In general, the studies had maximum times to initiate therapy of 6, 8, 12, or 24 hours. Some studies treating patients with posterior circulation strokes had longer time intervals of up to 48 hours. Not all studies presented the mean time to begin therapy, and some presented only the time to recanalization.

All studies documented the site of arterial occlusion by angiogram. The occlusions involved the internal carotid artery in 85 cases (33 cervical portion), middle cerebral artery in 570 cases (most cases, M1 or M2 segments; 47 were T

### Table 1. Studies and Number of Patients in the IAT and Control Groups

<table>
<thead>
<tr>
<th>Study</th>
<th>IAT, n</th>
<th>Control Subjects, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barr et al, 1994</td>
<td>12</td>
<td></td>
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<tr>
<td>Becker et al, 1996</td>
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<tr>
<td>Bendszus et al, 1998</td>
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<tr>
<td>Bockenheimer et al, 1991</td>
<td>18</td>
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<tr>
<td>Castro et al, 1996</td>
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<tr>
<td>Cross et al, 1997</td>
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<tr>
<td>Edwards et al, 1999</td>
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<tr>
<td>Endo et al, 1998</td>
<td>21</td>
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<tr>
<td>Ernst et al, 2000</td>
<td>16</td>
<td></td>
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<tr>
<td>Ezura and Kagawa, 1992</td>
<td>11</td>
<td></td>
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<tr>
<td>Furlan et al, 1999</td>
<td>108</td>
<td>54</td>
</tr>
<tr>
<td>Hacke et al, 1988</td>
<td>43</td>
<td>22</td>
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<tr>
<td>Kidwell et al, 2002</td>
<td>89</td>
<td></td>
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<tr>
<td>Lewandowski et al, 1999</td>
<td>22</td>
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<tr>
<td>Matsumoto and Satoh, 1991</td>
<td>50</td>
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<td>Mitchell et al, 1997</td>
<td>16</td>
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<td>Mori, 1991</td>
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<tr>
<td>Sasaki et al, 1995</td>
<td>44</td>
<td></td>
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<tr>
<td>Suarez et al, 1996</td>
<td>54</td>
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<tr>
<td>Ueda et al, 1999</td>
<td>76</td>
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<tr>
<td>Umemura et al, 2000</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Urbach et al, 1997</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Yabumoto et al, 1991</td>
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<td>Yamanome et al, 1999</td>
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<tr>
<td>Zeumer et al, 1998</td>
<td>61</td>
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<tr>
<td>del Zppo et al, 1988</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>del Zppo et al, 1997</td>
<td>26</td>
<td>14</td>
</tr>
</tbody>
</table>

*Some data on these patients were obtained from Bruckmann et al.†Some data on these patients were obtained from Mori et al.

with posterior circulation strokes had longer time intervals of up to 48 hours. Not all studies presented the mean time to begin therapy, and some presented only the time to recanalization.

All studies documented the site of arterial occlusion by angiogram. The occlusions involved the internal carotid artery in 85 cases (33 cervical portion), middle cerebral artery in 570 cases (most cases, M1 or M2 segments; 47 were T

### Table 2. Medications Used and Dose Ranges

<table>
<thead>
<tr>
<th>Medication</th>
<th>n (%)</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA urokinase</td>
<td>472 (55.4)</td>
<td>0.02–2×10^6 U</td>
</tr>
<tr>
<td>IA tPA</td>
<td>135 (15.8)</td>
<td>20–60 mg</td>
</tr>
<tr>
<td>IA prourokinase</td>
<td>134 (15.7)</td>
<td>6–9 mg</td>
</tr>
<tr>
<td>IA streptokinase</td>
<td>7 (0.8)</td>
<td>6–250×10^4 U</td>
</tr>
<tr>
<td>IA–IV tPA</td>
<td>50 (5.9)</td>
<td>IA up to 24 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV 0.6 mg/kg</td>
</tr>
</tbody>
</table>

*52 patients (6.1%) from 2 studies were treated with IAT, but a specific agent could not be accurately determined. Two patients (0.2%) from another study received both IA urokinase and IA tPA.
occlusions, which involve distal internal carotid artery, middle cerebral artery, and anterior cerebral artery), and vertebrobasilar system in 176 cases (including proximal, middle, distal basilar, bilateral distal, or proximal vertebral arteries). Isolated occlusion of the anterior cerebral artery (7 cases) and posterior cerebral artery (6 cases) was uncommon. Some occlusions were multiple (we counted the most distal), and in some cases, information about the specific site of occlusion was not available. The mean recanalization rate with IAT was 72.2%, with a range of 35.5% to 100% in individual studies.

Outcomes are presented in Table 3. Favorable outcomes were significantly more frequent in the IAT group than in the control group (41.5% versus 23%, P=0.002), with a significantly lower mortality rate (27.2% for IAT versus 40% for control group, P=0.004). The relative percent increase in the number of favorable outcomes in the IAT group compared with the control group was 80%. The IAT group had an OR of 2.4 (95% CI, 1.45 to 3.85) for favorable outcome and 0.56 (95% CI, 0.36 to 0.87) for death compared with the control subjects. There were significantly more SICHs in the IAT group compared with the control group (9.5% versus 3%, P=0.046). The IAT group had an OR of 3.4 (95% CI, 1.05 to 11.1) for SICH. The percent of SICH cases followed by fatal outcome was 40% (24 of 60) for the SICH cases for which this information was available.

In the IAT group, strokes were supratentorial in 488 (57.3%) and infratentorial in 157 cases (18.4%). In the remaining 207 cases (24.3%), either the specific localization or the information on favorable outcome, SICH, and death for the subset of patients was not available. In the control group, strokes were supratentorial in 78 (78%) and infratentorial in 22 cases (22%). Compared with the subgroup with infratentorial strokes, the patients with supratentorial strokes had a lower mortality rate (21.7% versus 54.1%; P<0.001; OR, 0.24; 95% CI, 0.16 to 0.35) and were more likely to have a favorable outcome (42.2% versus 25.6%; P=0.001; OR, 2.0; 95% CI, 1.33 to 3.0). Among the patients treated with IAT, there was no difference in the occurrence of SICH on the basis of stroke location (8.4% supratentorial versus 7.6% infratentorial; P=0.8; see Table 4).

A subanalysis of patients with supratentorial strokes receiving IAT (n=488) compared with control subjects with the same stroke location (n=78) and likewise for infratentorial strokes (n=157 for IAT and n=22 for control subjects) is presented in the Figure. Stroke territory did not appear to have a major influence on the efficacy of IAT because patients with either supratentorial or infratentorial strokes did better than control subjects.

Two studies used combined IVT/IAT and had data available for comparison, with a total of 28 patients (all with supratentorial strokes). The combined IVT/IAT subgroup was compared with the subgroup of patients with supratentorial strokes treated with IAT alone (459 patients). There was no significant difference in the occurrence of SICH (8.3% for IAT alone versus 10.7%, P>0.5) or death (21.7% for IAT alone versus 21.4, P>0.5), but there was a trend toward more favorable outcomes in the combined IAT/IVT subgroup (53.6% versus 41.5%, P=0.17) than in the IAT alone subgroup.

**Discussion**

This analysis shows that IAT is efficacious for some patients with AIS. The 18.5% absolute increase in the number of favorable outcomes between the IAT and control groups is even more positive than the results of the NINDS rt-PA study and the PROACT II study. The NINDS rt-PA study showed that 39% of the patients who received IVT had modified Rankin Scale scores of 0 to 1 at 90 days compared with 26% in the placebo group, an absolute difference of 13%. In the PROACT II study, for the patients treated as allocated, the absolute difference in the number of patients with modified Rankin Scale scores of 0 to 2 was 13.9%, favoring the intra-arterial prourokinase group compared with the controls.

The PROACT II study was restricted to patients with middle cerebral artery strokes. In our study, patients with infratentorial strokes, which tend to have worse outcomes, were present in both the IAT and the control groups. Mortality in historical control subjects with basilar or bilateral vertebral arteries occlusion can be 75% to 100%. Intervention with IAT may be even more beneficial in these

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**Table 3. Comparison Between IAT and Control Groups**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>IAT (n=852), %</th>
<th>Control Subjects (n=100), %</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome</td>
<td>41.5</td>
<td>23</td>
<td>2.4 (1.45–3.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>SICH</td>
<td>9.5</td>
<td>3</td>
<td>3.4 (1.05–11.1)</td>
<td>0.046</td>
</tr>
<tr>
<td>Death</td>
<td>27.2</td>
<td>40</td>
<td>0.56 (0.36–0.87)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

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**Table 4. Comparison Between Subgroups With Supratentorial and Infratentorial Strokes**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Supratentorial (n=488), %</th>
<th>Infratentorial (n=157), %</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome</td>
<td>42.2</td>
<td>25.6</td>
<td>2.0 (1.33–3.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>SICH</td>
<td>8.4</td>
<td>7.6</td>
<td>1.11 (0.56–2.2)</td>
<td>0.8</td>
</tr>
<tr>
<td>Death</td>
<td>21.7</td>
<td>54.1</td>
<td>0.24 (0.16–0.35)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
patients than in those with supratentorial strokes. The maximal time windows for beneficial results may differ in supratentorial and infratentorial strokes.

The increased risk of SICH with IAT compared with control subjects did not translate into increased mortality. The 9.5% occurrence of SICH in the IAT group is higher than the 6.4% in the NINDS study and the 4.6% rate seen in a large phase IV study of intravenous rtPA but is similar to the 10.2% rate seen in the PROACT II study. Because SICH tends to occur in patients with more severe strokes, the higher rate of SICH with IAT may simply reflect stroke severity. For example, the patients from the PROACT II study had higher National Institutes of Health Stroke Scale scores than those from the NINDS rt-PA trial (median, 17 versus 14). Baseline National Institutes of Health Stroke Scale scores were available in only 8 studies of our analysis, but clinical descriptions of the baseline status were present in most studies and suggested severe strokes in most of the cases. Another important factor may be the prolonged treatment time window, which was associated with higher rates of SICH and IAT may simply reflect stroke severity. However, the expanded time window for beneficial results may differ in supratentorial and infratentorial strokes.

Comparisons of subgroups of patients receiving IAT based on stroke location with the corresponding control subgroups showed results equivalent to the all-location strokes. Statistical significance was lost for SICH and favorable outcomes in infratentorial strokes because of the small sample size, but the reduction in deaths favoring IAT remained significant. The increase in favorable outcomes favoring IAT in supratentorial strokes also remained statistically significant.

Combining IVT with IAT may enhance efficacy, but the number of patients available for comparison was too small to achieve statistical significance. The 1 randomized study that compared IAT alone with combined IVT/IAT found no differences in neurological outcome or occurrence of SICH, although mortality was increased in the combined IAT/IVT group (29% versus 5.5%, P = 0.06). Their results, however, reflect the intention-to-treat analysis. Considering the patients who received medication, there would be an 18.3% absolute difference in the number of patients with modified Rankin Scale scores of 0 to 2 in 90 days favoring the IAT alone group (60% versus 41.7% in the combined IVT/IAT group).

One major advantage of IAT is the possibility of extending the treatment window for thrombolytic therapy. The delivery of the drug directly into the occluded vessel may also reduce the systemic effects of the thrombolytic agents. This may be particularly useful for patients who had recent surgery. Medication doses can be titrated, and the effects can be assessed during the intervention. However, the expanded time window may be offset by the time required for the angiographic procedure. IAT requires more personal and technical resources. This reduces the number of hospitals capable of offering this type of therapy and delays treatment, thereby potentially limiting its efficacy and use in large numbers of patients.

Our study has limitations that are inherent in any analysis of data from different sources. The studies are heterogeneous in their design, entry criteria, and end points. The lack of specific information in some trials caused their exclusion from our analysis. Most of the studies are case series, many are retrospective, and few are randomized trials. The studies found in the literature may represent some publication bias because trials with positive results are more likely to be published. We excluded small case series because they may not accurately represent the overall treatment experience. We did not include abstracts because they lacked sufficient details for our analyses. Some studies are published in journals that are not indexed, making access to them difficult. Most patients were treated with urokinase, which is not currently available in the United States but may be reintroduced in the near future. Despite all of these potential limitations, it is interesting to note that our results are very similar to the PROACT II study results and the Australian Urokinase Stroke Trial. Over a 2-year period, 200 patients will be randomized to receive either IAT with urokinase plus anticoagulants or anticoagulants alone. These studies will certainly contribute to the evaluation of IAT in stroke patients.

Our study may be helpful for addressing the issue of efficacy and safety of IAT for ischemic stroke because there are very limited data from large, randomized trials. A nonrandomized phase II trial of combined IVT/IAT for AIS, the Interventional Management of Stroke Study, started enrollment in February 2001. Another study, the Australian Urokinase Stroke Trial, is evaluating the use of IAT for acute posterior circulation ischemic stroke. Over a 2-year period, 200 patients will be randomized to receive either IAT with urokinase plus anticoagulants or anticoagulants alone. These studies will certainly contribute to the evaluation of IAT in stroke.

In summary, IAT appears to be an efficacious treatment option in selected patients at centers where staff and technical resources are available to administer it safely and efficiently. There are concerns about the relatively high rate of SICH in patients treated with IAT. In the United States, rtPA is the only currently available and approved thrombolytic agent for use in stroke patients. It is anticipated that results from ≥1 prospective, randomized trials will definitively address the issue of IAT as a treatment for AIS.
Acknowledgments
We are very grateful to Petra Fey for translating the studies published in German and to the PROACT II Investigators for providing unpublished data from the PROACT II study.

References


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