Hemorrhagic Complications After Off-Label Thrombolysis for Ischemic Stroke

Aitziber Aleu, MD; Patricio Mellado, MD; Christoph Lichy, MD; Martin Köhrmann, MD; Peter D. Schellinger, MD, PhD

Background and Purpose—Only 2% to 4% of patients with acute ischemic stroke receive thrombolytic therapy resulting from the current strict inclusion criteria among other issues. Safety of intravenous and intraarterial thrombolysis in off-label situations is controversially discussed. We sought to review the reports on such patients regarding intra- and extracranial hemorrhage.

Summary of Review—A MEDLINE search for off-label uses of thrombolysis revealed reports on 273 patients treated with intraarterial or intravenous thrombolysis for ischemic stroke. Symptomatic intracranial hemorrhage occurred in 19 of 273 patients (6.95%) and extracranial hemorrhage in 17 of 273 (6.22%).

Conclusions—These data suggest that the overall bleeding risk in off-label thrombolysis may not be as high as presumed. However, the small number of patients in each group and the likely underreporting of worse outcomes preclude drawing any conclusion as to specific treatment recommendations. Selected patients might benefit, however, from thrombolysis in situations not currently considered in the inclusion criteria. To obtain a meaningful database, a registry for off-label thrombolysis should be created. (Stroke. 2007;38:417-422.)

Key Words: safety ■ symptomatic intracranial hemorrhage ■ thrombolysis

Treatment of ischemic stroke dramatically changed after the introduction of thrombolytic therapy in 1995. However, only 2% to 4% of the patients receive intravenous thrombolysis (IVT) mainly as a result of the short time window and the strict inclusion criteria.

As experience with tissue plasminogen activator (tPA) increases, new situations emerge in which the safety of thrombolysis remains unknown. Moreover, the inadvertent or deliberate off-label use of thrombolysis has led to a requestioning of some of the stated exclusion criteria. In these 10 years of experience with tPA, many articles have been published on doubtful situations in which patients were treated.

Our aim was to review the literature regarding hemorrhagic complications after off-label situations despite IVT or intraarterial thrombolysis (IAT) being administered to date.

Methods
We searched MEDLINE and GOOGLE SCHOLAR entries between December 1995 and March 2006 for any published data on off-label use of IVT or IAT for stroke or other indications despite presumed high risk of hemorrhage. The search terms were “thrombolysis,” “hemorrhage,” and the protocol exclusions listed in the randomized controlled trials (RCTs) of IVT and IAT; finally, we searched for other off-label situations of clinical relevance not considered in RCTs. Reference lists in all articles were checked for further references. Both English and non-English articles or abstracts were included.

For practical purposes, assuming different levels of interest for stroke clinicians, we established three groups.

In the first group, we searched for symptomatic intracranial hemorrhage (SICH) after off-label IVT or IAT for stroke. Most of these off-label uses, but not all, represent exclusion criteria from the original RCT: brain tumors, intracranial vascular malformations, recent ischemic stroke, previous intracranial hemorrhage, severe head trauma, previous neurosurgery, uncontrollable hypertension, hyperglycemia, abnormal baseline coagulation, low platelet count, or seizures. The other off-label uses were not specific exclusion criteria in RCT but represent unknown situations in which safety of IVT or IAT cannot be assumed; these included: intracranial and extracranial dissections, amyloid angiopathy, endocarditis, and microbleeds. For each situation—exclusion criteria or unknown use—we searched for SICH after IVT or IAT for stroke. Additionally, for each situation, we searched for SICH after off-label thrombolysis for other uses, eg, myocardial infarction (MI) or pulmonary embolism (PE). We included nonstroke uses exceptionally in this group to gather as much safety data as possible. For example, thrombolysis for MI in patients with brain tumors or thrombolysis for PE in patients with intracranial aneurysms may elucidate the risk of IVT in such excluded conditions. To avoid confusion, these data are not considered in the total amount of patients and are presented separately.

In a second group, we searched for extracranial hemorrhages (EH) after off-label use of IVT or IAT for ischemic stroke. Like in the former group, contraindications from RCT are listed first, eg, stroke after recent surgery, recent gastrointestinal or genitourinary hemorrhage, recent MI or pericarditis, and other situations are listed second, eg, aortic dissection or aneurysm and polytrauma.

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TABLE 1. SICH After Off-Label Thrombolysis for Ischemic Stroke

<table>
<thead>
<tr>
<th>Off-Label Situation</th>
<th>n</th>
<th>IVT</th>
<th>IAT</th>
<th>SICH</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial vascular malformations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aneurysms</td>
<td>31</td>
<td>2</td>
<td>29</td>
<td>3</td>
<td>12–20</td>
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<tr>
<td>Arteriovenous fistulae</td>
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<td>0</td>
<td>5</td>
<td>0</td>
<td>26–28</td>
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<tr>
<td>Anatomic variants</td>
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<td>0</td>
<td>2</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Previous neurosurgery</td>
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<td>3</td>
<td>2</td>
<td>37</td>
</tr>
<tr>
<td>Previous stroke</td>
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<td>1</td>
<td>0</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>Abnormal coagulation/platelets</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>2</td>
<td>33, 35, 36</td>
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<td>Severe head trauma</td>
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<td>1</td>
<td>1</td>
<td>2</td>
<td>39–33</td>
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<tr>
<td>Hypertension</td>
<td>30</td>
<td>30</td>
<td>0</td>
<td>3</td>
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<td>0</td>
<td>1</td>
<td>43</td>
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<tr>
<td>Endocarditis</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>44</td>
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<tr>
<td>Microbleeds</td>
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<td>5</td>
<td>19</td>
<td>2</td>
<td>46–48</td>
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<td>Dissections</td>
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<td>Intracranial</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>49</td>
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<tr>
<td>Extracranial</td>
<td>68</td>
<td>50</td>
<td>18</td>
<td>1</td>
<td>50–55</td>
</tr>
</tbody>
</table>

Note: Off-label situations for which no patients were found are not listed in this table.

A third group was created for special off-label situations such as pregnancy and childhood in which there may be risk of either SICH or EH.

We deliberately excluded data concerning thrombolysis for stroke in patients over 80 years of age, because information on this is already available in published data. Moreover, this age group was considered a contraindication only in some thrombolytic trials.

Results
We found 273 patients who received off-label IVT or IAT for ischemic stroke. Hemorrhagic complications occurred in a total of 36 patients, SICH in 19 of 273 patients (6.95%) and EH in 17 of 273 (6.22%). Concerning patients treated with IVT or IVA for other uses than stroke, 18 patients were identified, one of whom developed a SICH.

SICH After Off-Label Thrombolysis (Tables 1 and 2)

Intracranial Aneurysms and Vascular Malformations
Thirty-one patients with intracranial aneurysms treated with thrombolysis for ischemic stroke were found. IVT was performed in 2 patients11,12 and IAT in 29 (24 with urokinase [UK],13–17 4 with tPA,15,18,19 and one with both UK and tPA20). SICH occurred in 3 patients treated with IAT (2 with UK, one with tPA), with 2 being subarachnoid hemorrhages.16–18 Thrombolysis for nonstroke uses in patients with intracranial aneurysms has been reported in 4 patients: 3 patients with intracranial aneurysms (coiled, clipped, and untreated, respectively) received IVT for MI21,22; the patient with an untreated aneurysm experienced a subarachnoid hemorrhage.21 The fourth patient with a coiled aneurysm was safely treated for PE with local thrombolysis with tPA and thrombus fragmentation.23

Concerning thrombolysis in patients with intracranial arteriovenous malformations, 2 patients were found; IAT with tPA for ischemic stroke was safely used for a middle cerebral artery embolism during diagnostic angiography24 and IVT for PE was safely given to a patient with an unruptured arteriovenous malformation.25

Five patients with cerebral arteriovenous fistulas complicated by venous thrombosis were safely treated with IAT using UK.26–28 Two patients with vascular anomalies (middle cerebral artery fenestration and trigeminal artery persistence) safely received IAT with UK for stroke.29

We did not find any report on patients with cavernoma treated with IVT or IAT for stroke or other indications.

Brain Tumors
We did not find patients treated with IVT or IAT for stroke despite the presence of an intracranial tumor. Neither did we find patients treated with thrombolysis in whom an intracranial tumor was overlooked initially. Four patients treated with thrombolysis for nonstroke indications were found; 3 of them received IVT for MI (2 with a meningioma and one with a pituitary adenoma); one experienced a SICH,30,31 and the fourth patient who had a meningioma was safely treated with local thrombolysis for deep venous thrombosis.32

Previous Ischemic Stroke Within 3 Months or Previous Intracranial Hemorrhage
IVT in patients with recent stroke has been reported in 2 patients; both had a stroke 2 weeks before treatment and developed an SICH.33 We did not find any report of thrombolysis for ischemic stroke or nonstroke indications in patients with a history of intracranial hemorrhage. A patient with an overlooked subdural hematoma who received IVT for stroke developed a fatal ICH.34

Low Platelet Count and Abnormal Baseline Coagulation
IVT for stroke was performed in a patient with a platelet count of 52,000/mm³ who developed SICH.33 In another patient, whose initial and repeated platelet counts were 13,000/mm³ and 29,000/mm³, IVT was performed, because additional analysis revealed pseudothrombocytopenia with the corrected count being 143,000/mm³.35 We found 9 patients treated despite abnormal baseline coagulation (prothrombin time >15 s or international normalized ratio >1.5); one experienced an SICH.33,36 We did not find data on patients treated with full-dose low-molecular-weight heparin who received IVT or IAT for ischemic stroke.

Previous Neurosurgery
Three patients with a recent craniotomy were treated with IAT for stroke; 2 of them experienced a fatal SICH.37 No report was found on extraventricular drainage or ventriculoperitoneal shunt and thrombolysis for ischemic stroke. Nine
patients who developed PE after neurosurgery were safely treated with local thrombolysis with UK.38

**Severe Head Trauma**

A patient with a right middle cerebral artery stroke who subsequently fell and experienced a severe head trauma developed an acute subdural hematoma after IAT.39 Another patient with a severe head trauma 2 weeks before the stroke experienced a fatal SICH after IVT.33

**Hyperglycemia >22.22 mmol/L or Hypoglycemia <2.77 mmol/L**

We did not find any report on such patients treated with IVT or IAT for stroke.

**Systolic Blood Pressure >185 mm Hg or Diastolic Blood Pressure >110 mm Hg**

IVT was performed in 30 patients despite hypertension; 3 experienced an SICH and one an asymptomatic intracranial hemorrhage.33,36,40,41

**Improving or Minor Neurologic Deficit**

We found 19 patients treated with IVT despite improving neurological symptoms; none of them had a SICH.81 Studies have shown that 32% to 34% of patients who do not receive thrombolytic therapy because of clinical improvement are more likely to experience subsequent neurologic worsening.3,42

**Seizures**

One patient with a focal seizure and secondary generalization at stroke onset was safely treated with IVT for ischemic stroke.43

**Arterial Puncture in a Noncompressible Site in the Previous 7 Days**

We did not find any report on this protocol exclusion.

**Endocarditis**

One patient with bacterial endocarditis was safely treated with IAT for stroke using UK.44

**Amyloid Angiopathy**

No patients with histologically verified amyloid angiopathy treated with IVT or IAT for stroke were found. Recent data on 50 patients with intracranial hemorrhage after thrombolysis for MI revealed 10 patients with pathologically confirmed amyloid angiopathy.45

**Microbleeds**

We found 24 patients in which microbleeds were diagnosed by magnetic resonance imaging before thrombolysis.46–48 Five patients received IAT and 19 IVT; SICH occurred in one patient of each group.

**Intracranial and Extracranial Dissections**

One patient with an intracranial internal carotid artery dissection safely received IAT with UK plus extracranial bypass.49

Concerning thrombolysis for stroke after extracranial carotid dissections, 68 patients were treated, 50 with IVT50–54 and 18 with IAT. In the IVT group, none of the patients developed a rupture of the dissected vessel or subarachnoid hemorrhage; one patient developed an SICH51 Mortality was 13% and favorable outcome with a modified Rankin Scale score 0 to 2 was observed in 60% of patients.54,55 In the IAT group (11 vertebral and 7 carotid dissections), 2 patients received tPA and 16 UK; no SICH occurred.51,55

**Extracranial Hemorrhage After Off-Label Thrombolysis for Ischemic Stroke (Table 3)**

**Recent Surgery**

Thrombolysis for a postoperative stroke was reported in 57 patients, all treated with IAT.77,76–99 SICH occurred in 3 patients (2 postcraniotomy, already mentioned). EH occurred in 9 patients: 2 hemothorax and one fatal pericardial tamponade after cardiac surgery and 6 minor surgical site bleedings after carotid endarterectomy, tracheostomy, cardiac, plastic, and urinary surgery, respectively.

**Gastrointestinal or Genitourinary Bleeding**

No patients with recent gastrointestinal or urinary hemorrhage and ischemic stroke treated with thrombolysis were found. A woman with a 1-year history of dysfunctional uterine bleeding, who received IVT for stroke, developed a uterine hemorrhage requiring emergency uterine artery ligation. Although menstruation is not a contraindication, we found 5 women who safely received tPA for stroke.60

**Recent Myocardial Infarct or Pericarditis**

Five patients with recent or concomitant MI received thrombolysis for stroke, 4 IVT and one IAT with UK; 3 patients died from cardiac tamponade.61–63

**Aortic Dissection or Aneurysm**

Three patients with aortic dissection received thrombolysis for stroke, two IVT and one IAT; one experienced an aortic rupture and required graft surgery.65 No data were found on patients who received IVT for stroke and died in which the necropsy revealed an amyloid angiopathy.

**Polytrauma**

A patient with open and closed limb fractures and blunt neck injury causing near occlusive internal carotid artery dissection who presented with fluctuating neurologic deficits was safely treated with IAT and stenting.67

**Extra- and Intracranial Hemorrhage After Thrombolysis for Ischemic Stroke in Pregnancy or Childhood (Table 4)**

**Pediatric or Adolescent Age**

Nine patients aged less than 18 years who received thrombolysis for ischemic stroke were reported57,68–73; 7 received IAT (3 with UK, 4 with tPA) and 2 IVT; one developed an
asymptomatic intracranial hemorrhage. A 3-year-old girl with PE and concomitant cerebral infarction 3 weeks after cardiac surgery safely received IVT and IAT with tPA along with mechanical embolus fragmentation.

**Pregnancy**

Thrombolysis for stroke has been reported in 11 women, one SICH occurred after 5 IVT and 6 IAT. Nine were treated in the first trimester, most inadvertently, and 2 in the third trimester. Of the 5 patients receiving IVT, none developed SICH and one intrauterine hematoma occurred. In the 6 patients receiving IAT (2 with tPA, 4 with UK), an intravenous catheter-related hematoma, buttok hematoma, and one SICH occurred. Of the 11 fetuses, 5 were delivered at term and 6 died. Of these 6, one died at the mother’s death and another 3 because the mothers elected an induced abortion; the others were miscarriages after UK administration (one had lethal chromosomal anomalies at autopsy).

**Discussion**

This review aims to give the stroke clinician a quick overview of what has been done in off-label or doubtful situations. It may also suggest future trials or registries. It is not the aim of this review to encourage the use of thrombolysis in these specific situations.

We found 71 reports with 273 patients in whom thrombolysis for ischemic stroke was performed despite contraindications resulting from a perceived positive risk–benefit ratio. We assume that there is both an underreporting and a publishing bias; most likely only cases with better outcomes are reported.

Our review precludes to draw any definitive general conclusions because the number of patients for each situation is small; clearly, further studies are needed. In some situations, however, in which the number of patients is relatively high, eg, dissections, microbleeds, or postoperative strokes (except postsurgical bleeding), complications may not be as high as expected.

Concerning microbleeds, the results of the BRASIL study showed that neither the presence nor the number of microbleeds was associated with SICH. Consequently, data on microbleeds suggest relative safe use of thrombolysis.

In summary, the decision to use off-label thrombolysis for stroke should be individualized according to existing protocols, individual patient situation, and family consent. We would like to emphasize the reporting of such patients, because most of these uncommon clinical situations cannot be studied in a RCT as a result of their low prevalence. For those situations, we propose an international registry in which patients could be reported to freely with the intent of gathering information for future recommendations in rare and unusual stroke situations. Regarding situations with a higher prevalence that were excluded in the original RCT such as pregnancy or childhood, further RCTs are necessary to establish the safety of thrombolysis. Finally, we would like to point out that in strokes after cervicocephalic artery dissections and microbleeds, perhaps wrongly perceived as bleeding-prone conditions, data suggest safe use of thrombolysis.

**Disclosures**

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