Safety of Intra-Arterial Thrombolysis in the Postoperative Period

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Background and Purpose—Limited systemic fibrinolysis and reduced dosage are features of intra-arterial thrombolysis (IAT) that may be advantageous in the treatment of postoperative strokes. However, IAT may increase the risk of surgical bleeding. We sought to determine the safety of postoperative IAT.

Methods—This was a retrospective case series from 6 university hospitals. All cases of IAT within 2 weeks of surgery were identified. Demographics, stroke mechanism, stroke severity, imaging and angiographic findings, time between surgery and lysis, thrombolytic agent used, surgical site bleeding, intracranial bleeding, and mortality rates were determined. Death or complications directly related to IAT were determined.

Results—Thirty-six patients (median age, 71.5 years; range, 45 to 85) were identified. Median time from surgery to stroke was 21.5 hours (range, 1 to 120). Open heart surgery was done in 18 (50%), carotid endarterectomy in 6 (17%), craniotomy in 3 (8%), ophthalmic– ear, nose and throat surgery in 2 (6%), urologic-gynecologic surgery in 4 (11%), orthopedic surgery in 2 (6%), and plastic surgery in 1 (3%). The stroke causes were cardioembolism in 24 (67%), large-vessel atherosclerosis in 4 (11%), dissection in 3 (8%), postendarterectomy occlusion in 4 (11%), and radiation arteriopathy in 1 (3%). Median time to angiogram was 2.5 hours (0.1 to 5.5). Occlusion sites were M1 in 19 (53%), M2 in 9 (25%), internal carotid artery in 5 (14%), basilar artery in 2 (6%), and posterior communicating artery in 1 (3%). Thrombolysis was completed at a median of 4.5 hours (range, 1 to 8.0). Tissue plasminogen activator was used in 19 (53%) and urokinase in 17 (47%). Nine (26%) patients died. Surgical site bleeding occurred in 9 (25%) cases (minor in 6, major in 3). The major surgical bleeds were 2 post–craniotomy intracranial hemorrhages and 1 hemopericardium after coronary artery bypass grafting; all were fatal. Six deaths were non-IAT related: 3 caused by cerebral edema and 3 by systemic causes. Major bleeding complications were significantly more common among patients with craniotomy (P<0.02).

Conclusions—Postoperative IAT carries a risk of bleeding in up to 25% of patients but is usually minor surgical site bleeding. Avoiding IAT in intracranial surgery patients may reduce complications. Mortality rate in this series was similar to that reported in prior IAT trials. IAT remains a viable therapeutic option for postoperative strokes. (Stroke. 2001;32:1365-1369.)

Key Words: complications ■ retrospective studies ■ stroke management ■ thrombolysis

The risk of ischemic stroke is increased during the postoperative period. It is estimated that stroke occurs in up to 2.9% of all patients who undergo general surgery.1 Even patients who undergo noncardiac, noncarotid surgery have an increased risk of stroke.1 Stroke in the postoperative period is usually due to underlying comorbid conditions rather than surgical or anesthetic complications. In addition, immobility and release of thrombogenic substances after tissue injury lead to a procoagulant state that may increase the risk of stroke.2 Anticoagulants used for stroke prevention are often held before surgery, increasing the risk of stroke in the perioperative period.

Management of stroke in the postoperative period is difficult. Intravenous thrombolysis is contraindicated in the first 2 weeks after surgery.3 Intra-arterial thrombolysis (IAT) uses a lower dose and local delivery of lytic agent and...
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<table>
<thead>
<tr>
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<th>9 (25%) total</th>
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<tbody>
<tr>
<td>Fatalities</td>
<td></td>
</tr>
<tr>
<td>Death caused by IAT-related bleeding</td>
<td>3 (8%) (1 pericardial tamponade, 2 intracranial hemorrhages)</td>
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<tr>
<td>Death not related to hemorrhage</td>
<td>6 (17%) (3 cerebral edema, 1 MI, 1 sepsis, 1 respiratory failure)</td>
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<tr>
<td>IAT-related surgical site bleeding (nonfatal)</td>
<td>6 (17%) total</td>
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<td></td>
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<tr>
<td></td>
<td>1 skin flap bleed after plastic surgery</td>
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<td></td>
<td>1 incision site bleed after urologic surgery</td>
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<td></td>
<td>1 stoma bleed after tracheostomy</td>
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<tr>
<td></td>
<td>2 neck hematomas after CEA</td>
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<tr>
<td>Intracranial hemorrhage</td>
<td>9 (25%) total</td>
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<tr>
<td></td>
<td>3 (8%) symptomatic (2 in postcraniotomy patients)</td>
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<tr>
<td></td>
<td>6 (17%) asymptomatic</td>
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IAT indicates intra-arterial thrombolysis; MI, myocardial infarction; CEA, carotid endarterectomy; and CABG, coronary artery bypass grafting.

accomplishes clot-specific lysis of occlusive thrombi with limited systemic plasminogen activation and may therefore be a viable therapeutic option in postoperative stroke patients. Although several centers use IAT for this purpose, the reported experience is limited.4,5 In this study, we sought to determine the safety of IAT for stroke in the postoperative period.

Subjects and Methods

This is a retrospective case series study from 6 university hospitals with the infrastructure to perform neurovascular interventional procedures. The investigators reviewed their stroke databases, selecting all patients in whom IAT had been performed in the first 2 weeks after any type of surgery. Demographics, stroke risk factors, clinical syndrome, stroke location, stroke mechanism, National Institute of Health Stroke Scale (NIHSS) score, CT findings, time of stroke with relation to surgery, type of surgery, time to IAT, angiographic findings, thrombolytic agent, and dose used, recanalization results by TIMI classification,6 systemic or intracranial bleeding, and clinical outcome were abstracted from the chart or the database. Determination of middle cerebral artery territory involvement exceeding one third was done by investigators at each site not using a formal algorithm. When the NIHSS was unavailable, the investigators retrospectively obtained it by reviewing the medical records in accordance with prior studies.7 Coagulation studies were reviewed to detect any abnormality (low platelets or prolonged partial thromboplastin time or INR). The investigators specifically reviewed the records for complications that may have directly resulted from thrombolysis: intracranial hemorrhage, systemic bleeding (at the surgical site or elsewhere), and need for transfusion or any other measures to achieve hemostasis. Bleeding was classified as major if it led to death or required transfusion. Symptomatic intracranial bleeding was also classified as major. When death occurred, it was determined whether it was due to surgical site bleeding, systemic nonsurgical site bleeding, intracranial hemorrhage, cerebral edema secondary to the stroke, or other medical conditions. The clinical outcome was determined by use of the discharge Rankin Scale and the 7-day and 30-day NIHSS when available.

Statistical Analysis

Statistical analysis was performed with STATA version 5.0 (Stata Corporation, College Station, Tex). Bivariable comparisons were performed by means of Fisher’s exact test to determine whether the risk of bleeding complications was associated with surgical site, timing of IAT in relation to surgery, or choice of thrombolytic agent. Planned multivariable analysis was not performed because only one variable emerged from the bivariable analyses.

Results

A total of 36 patients were treated with IAT for ischemic stroke in the postoperative period. There were 23 (69%) men and 13 (31%) women; age ranged from 45 to 85 years, with a median of 71.5 years. The stroke mechanism was cardioembolism in 24 (67%), large- vessel atherosclerosis in 4 (11%), occlusion after endarterectomy in 4 (11%), dissection in 3 (8%), and radiation arteriopathy in 1 (3%). The surgical procedure was open heart surgery in 18 (50%), carotid endarterectomy in 6 (17%), craniotomy in 3 (8%), ear, nose and throat–ophthalmic surgery in 2 (6%), orthopedic surgery in 2 (6%), and plastic surgery in 1 (3%). General anesthesia was used in 33 (92%) patients and local–regional anesthesia in 3 (8%). The median time between surgery and stroke onset was 21.5 hours (range, 1 to 120 hours). The median NIHSS was 17 (range, 5 to 25). Initial elevated blood pressure above the NINDS parameters for intravenous thrombolysis was present in 6 patients (17%); pharmacological reduction was necessary in 2, and spontaneous reduction occurred in 4.

Early CT evidence of ischemia was present in 13 (36%) patients. CT involvement exceeding one third of the middle cerebral artery (MCA) territory was seen in 2 (6%) patients. Hemispheric edema was present in 7 (19%) patients. Abnormal coagulation studies were present in 3 (8%) patients: platelets <100 000 in 2 patients and INR >1.7 in 1 patient.

The median time to angiogram was 2.5 hours (range, 10 minutes to 5.5 hours) after stroke onset. The occluded vessel was the M1-MCA in 19 (53%) patients, the M2 or an MCA branch in 9 (25%), the internal carotid artery in 5 (14%), the basilar artery in 2 (6%), and the posterior cerebral artery in 1 (3%). Tissue plasminogen activator (TPA) was used in 20 (56%) patients and urokinase (UK) in 16 (44%). The TPA dose used ranged from 9 to 40 mg, with a median dose of 21 mg. The median dose of UK was 500 000 U (range, 40 000 to 1 500 000). Thrombolytic infusion was completed at a median of 4.5 hours (range, 1 to 8) from stroke onset. TIMI recanalization was grade 3 in 14 (39%) patients, grade 2 in 16 (44%), and grade 0 to 1 in 6 (17%).
The complications of IAT are summarized in the Table. Surgical site bleeding occurred in 9 (25%) patients, which was fatal in 3 (8%) and minor in 6 (17%). The fatal surgical site bleeds included pericardial tamponade in a patient after coronary artery bypass grafting (CABG) and intracranial hemorrhages in 2 patients with recent craniotomy. The hemorrhage was ipsilateral to the craniotomy site in both cases. IAT after craniotomy was significantly associated with fatal outcome ($P<0.02$). The nonfatal surgical bleeds included bleeding from a skin flap in 1 patient, incisional bleeding in 1 patient after urologic surgery, stomal bleeding in 1 patient after tracheostomy, neck hematoma in 2 patients after carotid endarterectomy, and sternotomy bleeding in 1 patient after CABG. The neck hematomas did not compromise the airway and did not require any specific therapy. Transfusion in the absence of overt systemic bleeding occurred in 4 (11%) patients. Asymptomatic intracranial hemorrhage was detected on follow-up CT in 6 (17%) patients. Symptomatic intracranial hemorrhage occurred in 3 (8%) patients and was fatal in 2 (6%); both occurred after craniotomy. One nonfatal, symptomatic intracranial hemorrhage occurred in a patient after CABG. The 6 (17%) non–hemorrhage-related deaths were cerebral edema in 3, sepsis in 1, myocardial infarction in 1, and respiratory failure in 1. No hemorrhagic complications occurred in the patients with abnormal coagulation studies or elevated blood pressure before treatment.

There was no significant difference in the complication rate when patients with early (<24 hours after surgery) stroke and IAT were compared with patients with later stroke and IAT ($P=0.18$). In the TPA group, 6 of 19 patients had nonfatal surgical site bleeding, whereas in the UK group, 3 of 18 patients had nonfatal surgical bleeding. Fatal bleeding occurred in 2 patients in the TPA group and in 1 in the UK group. These differences between the TPA and UK groups did not achieve statistical significance ($P=0.45$). There was no relation between the extent of MCA territory involvement and the development of hemorrhagic complications.

The median NIHSS at 24 hours, available in 33 of 36 (94%) patients, was 6.5 (range, 0 to 42). The 7-day NIHSS, also available in 33 of 36 patients, was 8.5 (range, 0 to 42). The median Rankin score on discharge, available in 32 of 36 (89%) patients, was 3.5. Good outcome at discharge, defined by Rankin score $\leq 2$, was achieved by 12 of 32 (38%) of patients for whom the data were available.

**Discussion**

Postoperative strokes often occur when the patient is hospitalized, making IAT an attractive option. IAT has been performed in postoperative patients with pulmonary embolism without any serious complications. The management of postoperative stroke with IAT had been examined before in small case series but not in larger multicenter series. This is the first multicenter study to examine the safety of IAT in the postoperative period and is the largest series reported thus far.

In the postoperative period, poorly cross-linked fibrin at the surgical site could act as a binding site for thrombolitics, disrupting hemostasis and leading to bleeding. In our study, bleeding at the surgical site occurred in about 25% of patients, usually at the incision site and less commonly within the surgical bed itself. Incisional bleeding was controlled with local measures, did not require transfusion, and had no impact on outcome. Bleeding within the surgical bed itself carried a more ominous prognosis. In 1 patient, post-CABG fatal pericardial tamponade occurred even though the patient was being followed with serial echocardiograms to detect bleeding. Pericardial bleeding has been described in patients receiving intravenous TPA after myocardial infarction or pericarditis but did not occur in a small series of patients treated with IAT after CABG. Kasner et al described a case of hemopericardium complicating intravenous TPA therapy for acute stroke in a patient with possible post-CABG pericarditis. Because in our study the pericardial tamponade occurred 2 days after surgery, it is unlikely that post-CABG pericarditis explains the hemopericardium as this condition occurs later. Dysfunctional platelets have been described before in patients after CABG and could account for a hemorrhagic tendency. It is noteworthy that the IAT was performed on the first day after CABG, whereas most cases of post-CABG IAT reported in the literature have been later. Clot-bound fibrin in the hyperacute postoperative period may be less well polymerized and may pose a higher risk. Nevertheless, we did not find any relation between the time of stroke with relation to surgery and the complication rate when all the bleeding complications were analyzed. The low complication rate encountered in post-CABG patients is not surprising because similar results were reported in prior series.

IAT after craniotomy appears to have an unacceptable rate of major complications. In our series, 2 of 3 patients with recent craniotomy had a fatal intracranial hemorrhage, and this association achieved statistical significance. Obviously, the small size of the sample precludes firm conclusions, but IAT is probably not safe for patients with recent craniotomy.

The mortality rate in our series was 25%, similar to that reported in prior trials of IAT. This mortality rate is surprisingly low, considering that our patients had a high median age (71.5 years) and many were critically ill after undergoing surgery. Our sample was heterogeneous; patients with different occlusion sites were included, whereas prior trials limited enrollment to patients with specific occlusions and specific stroke syndromes. The incidence of systemic bleeding in prior series of intra-arterial thrombolysis is $<1%$. In our study, systemic bleeding occurred in 25% of patients and was fatal in 8%. Thus, systemic bleeding appears to be much more common in postoperative patients, although it is usually minor and responsive to local measures. The incidence of asymptomatic intracranial hemorrhage in our series (8%) was similar to that reported in prior trials. On the other hand, asymptomatic intracranial hemorrhage was only 17% in our study. This comparatively low rate of hemorrhage may be related to the presence of branch occlusions and posterior circulation infarcts in our series, with smaller infarcts and less risk of bleeding. In addition, CT interpretation and identification of petechial hemorrhage is known to vary widely among different readers. Enhanced thrombogenesis and impaired fibrinolysis in the postoperative period could account for the lower incidence of asymptomatic intracerebral hemorrhage.

Transfusion was necessary in 11% of our patients without evidence of overt bleeding. The cause of this drop in the hematocrit is unclear; possible culprits include surgical bleed-
ing before the stroke, low-grade gastrointestinal bleeding, or small retroperitoneal bleeding. A dilutional effect as a result of perioperative intravenous fluid administration could also account for a decrease in hematocrit.

The recanalization rate seen in our series was 39% for TIMI grade 3 and 44% for TIMI grade 2. The high recanalization rate seen may be related to the presence of branch occlusions and the reduced time to angiography when strokes occur in the hospital. This has important treatment implications because lower doses of thrombolytic agents may be needed in the postoperative period to achieve adequate recanalization. Mechanical manipulation of the clot, not routinely performed in thrombolyis trials, may also explain the high TIMI 3 and TIMI 4 recanalization rates. In addition, in our series, thrombolysis was individualized to the angiographic findings and the dose titrated to obtain optimal recanalization.

Clinical outcome was similar to that seen in prior IAT studies, with Rankin score ≤2 at 1 week in 38% of our patients. Thus, despite our patients being critically ill and having medical problems that could interfere with locomotion and activities of daily living, the functional outcome in postoperative IAT patients appears to be similar to that reported in prior IAT trials. UK and TPA have different pharmacological profiles, which could be of importance in treating postoperative patients. The short-action, clot-bound fibrin specificity and low immunogenic potential make TPA an ideal drug for IAT in the postoperative period. Nevertheless, we did not find any difference in the complication rate between these two agents in this study.

On the basis of this limited retrospective case series, IAT appears to be a viable therapeutic option for ischemic stroke that complicates the postoperative period. Hemorrhagic complications are frequent but usually are minor and self-limited. Comparison with prior thrombolytic trials is hampered by the heterogeneous sample studied and the different treatments used. Clinical efficacy, recanalization rates, and safety of IAT in the postoperative period should be studied in a prospective fashion.

Appendix: Principal Site Investigators
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References

Editorial Comment
Safety of Intra-Arterial Thrombolysis in the Postoperative Period
Intravenous tissue plasminogen activator (tPA) remains the only drug and route of administration approved in North America for acute stroke treatment. The narrow time window of efficacy, <3 hours from symptom onset, has limited the utility of this therapy in clinical practice. A recent evaluation of tPA use in the Cleveland area revealed that only 1.8% of all ischemic strokes were treated with this therapy. Efforts to improve prehospital delivery systems have resulted in some improvement in the percentage treated, but the vast majority of ischemic stroke patients are still excluded. Besides delays to presentation, patients are excluded from therapy even if they present within 3 hours of onset. Barber et
al identified that 27% of stroke patients arrived “in time” to the emergency department within 3 hours from onset. A vast majority of these “<3-hour” stroke patients were excluded from therapy because symptoms were deemed too mild (13.1%) or the patient was felt to be clinically improving (18.2%). Other important reasons for exclusion included CT abnormalities, premorbid status, and delays in stroke recognition. Recent surgery caused 1.6% of the <3-hour stroke population in this study to be excluded from systemic tPA treatment. In theory, the in-hospital stroke population should not be limited by delays in presentation, but unfortunately, most strokes in this setting are soon after surgery. Major surgery within the preceding 14 days is considered a contraindication for intravenous tPA, as outlined in the American Heart Association guidelines for stroke thrombolysis. Intra-arterial thrombolysis provides an alternative approach in ischemic stroke that has some evidence of efficacy based on the previously published Recombinant Prourokinase in Acute Cerebral Thromboembolism II (PROACT II) study. Local delivery of thrombolysis is well suited as a treatment in the immediate postoperative period. Such an approach uses small doses of thrombolytic at the site of arterial occlusion, limiting the systemic exposure of this therapy to the surgical bed.

In the preceding article, Chalela et al present the largest published series of postoperative stroke patients treated with intra-arterial thrombolytic therapy. Half of the series comprised patients who recently underwent open heart surgery and included other surgeries, such as endarterectomy; craniotomy; ophthalmologic/ear, nose and throat; urologic-gynecologic; orthopedic; and plastic surgery. All patients had angiography performed within 5.5 hours of symptom onset, with thrombolysis completed within 8 hours of symptom onset. Strokes included in this series all occurred within 5 days of surgery (median 21.5 hours). Two thirds of strokes were due to cardioembolic mechanisms.

Of the 18 open-heart surgery cases, only 1 patient had bleeding at the sternal incision; I suffered symptomatic intracranial hemorrhage and I developed fatal pericardial tamponade. Thrombolysis was performed early after open-heart surgery in the cardiac tamponade case, which may have affected risk of bleeding. This bleeding occurred despite close surveillance with daily echocardiograms after thrombolysis. Previous reports of 6 open-heart surgery cases revealed no significant bleeding, although all cases were ≈2 days after surgery. Most other bleeding was not considered life threatening, including 2 neck hematomas after endarterectomy and 1 sternal bleed after tracheostomy. Eleven percent of patients required transfusion.

The most compelling finding in this study was that 2 patients had fatal intracranial hemorrhage when receiving intra-arterial thrombolysis soon after craniotomy. Both hemorrhages were ipsilateral to the craniotomy site. Previous studies using thrombolysis after craniotomy in pulmonary embolism did not identify such a risk for intracranial hemorrhage when performed ≈7 days after neurosurgical procedure. This risk of serious intracranial bleeding (2 of 3) into the neurosurgical bed with local thrombolysis performed soon after surgery should be considered prohibitive.

Authors comment on recanalization frequency and outcome with intra-arterial thrombolysis. It is difficult to compare recanalization rates and outcomes with previously published trials due to the heterogeneity of the patients treated and the use of 2 different drugs (urokinase and tPA). One quarter of the occlusions treated in this study involved the internal carotid artery or posterior circulation vessels. The PROACT-II trial did not randomize patients with internal carotid artery or posterior circulation occlusion.

This study provides evidence that recent surgery should be considered a relative rather than absolute contraindication to thrombolysis and that decision making in this setting should be based on a careful case-by-case evaluation of the expected benefits and risks of the various available treatments. Thrombolysis has had a limited impact in stroke to date. We must evaluate these treatments in new stroke populations, which include the postsurgical group. I welcome and encourage a forward-thinking approach to these patients previously deemed “too risky” to treat but caution that such results are preliminary and require prospective evaluation. The most important goal of stroke thrombolysis is to find new reasons to treat rather than reasons not to treat. Only then will thrombolysis make a dramatic impact in stroke.

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