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Intra-arterial urokinase for acute ischemic stroke: Factors associated with complications

Article abstract—The authors abstracted the records of 43 patients treated with intra-arterial urokinase for acute ischemic stroke to identify predictors of serious complications. Sixteen (37%) had such a complication. Higher urokinase dose ($>1.5 \times 10^6$ U), higher mean arterial blood pressure before treatment (>130 mm Hg), basilar occlusive strokes, and severe strokes were most predictive of these complications. Although urokinase is no longer manufactured, these findings identify patients at risk for complications from other intra-arterial thrombolytics.

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A randomized trial is necessary to establish the efficacy of an acute intervention. However, predictors of complications of therapy can be identified by evaluating a series of patients treated with intra-arterial (IA) thrombolysis for acute ischemic stroke. Such predictors might identify patients for whom the high risk of IA thrombolysis makes a beneficial effect unlikely. This patient series, initially gathered as a quality assurance study, was analyzed to identify such predictors of complications.

Methods. All patients at two university-affiliated hospitals and one community hospital in which IA urokinase (UK, a drug no longer manufactured) was used for the treatment of acute cerebral arterial occlusion between June 1992 and April 1997 were identified and their medical records abstracted for information about complications and their possible predictors. The protocols for the use of UK were similar across hospitals. A time limit of 6 hours was set for the start of therapy in the anterior circulation, but not in the posterior circulation. Noncontrast head CT scan ruled out hemorrhage. Angiography confirmed the occluded artery. UK was then injected in 250,000-unit increments into the proximal end of the thrombus. Angiography was repeated between doses. Therapy was terminated one dose greater than necessary to achieve at least partial reperfusion of the vessel. Manual pressure was applied to the arterial puncture site for 15 minutes after catheter removal.

Functional status was rated using a modification of the Glasgow Outcome Scale (GOS), briefly summarized as: 1 = brain death or death; 2 = coma; 3 = awake, severe deficits; 4 = awake, moderate deficits; 5 = awake, mild deficits; and 6 = normal.[1] Complications were dichotomized as serious or not. Serious ones required surgery or blood products, were life threatening or led to death, or led to worsening clinical condition.

Statistical analyses included standard bivariate analyses using nonparametric methods and recursive partitioning as a nonparametric form of multivariate analysis.[2] Significance was set at two-sided $p \leq 0.05$. Analyses were performed using STATA (version 6, STATA Corporation, College Station, TX) and CART (version 3.5, Salford Systems, San Diego, CA). The Human Subjects Committee at the University of Washington and the Swedish Medical Center Providence Campus approved the study.

Results. Forty-three patients were identified. Their median age was 65 years (range 18 to 84). Sixty-seven percent were men, 19% were treated for stroke as a complication of angiography, and 28% had basilar artery occlusions. Prior to IA therapy, 16% of patients were comatose (GOS = 2) and 40% had severe deficits (GOS = 3). Mean arterial blood pressure (MAP) was 116 mm Hg (range 83 to 159), and 24% of the 34 available CT reports described ischemic changes. Of the 35 cases with time data available, median time to IA therapy was 5.2 hours (range 0.3 to 56). The median UK dose was 0.75×10^6 U (range 0.23 to 2.0). Sixteen of 43 patients (37%) had a serious complication (SC), including 3 of 8 patients (38%) treated for occlusive complications of diagnostic angiography. SC were associated with worse outcomes (median GOS = 3 versus GOS = 4, $p = 0.002$) and are described in the table.

Patients with SC compared with those without were more likely to have basilar occlusion (8/12 versus 8/31, $p =$

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Table *Serious complications and their outcomes*

Patient no.	Clinical scenario	Dose of UK, 10^6 U	Hospital outcome	Complication
1	ICA angiographic complication	1.25	Mild disability	Neck hematoma at site of recent surgery
2	MCA angiographic complication	0.5	Severe disability	Large hemorrhagic conversion of left brain infarct; died in nursing home 4 days after discharge
3	MCA angiographic complication	1.0	Died	Large right MCA distribution hematoma, also subdural and subarachnoid blood
4	ICA stroke	1.0	Severe disability	Left basal ganglia hemorrhage with extension into ventricles and subarachnoid space
5	MCA stroke	0.375	Mild disability	Hypotensive (SBP = 63) and bradycardic (HR = 34) during thrombolysis procedure
6	MCA stroke	0.75	Died	Left MCA distribution hemorrhagic infarct
7	MCA stroke	2.25	Moderate disability	Retroperitoneal hematoma
8	MCA stroke	2.25	Died	Right basal ganglia and temporal lobe hemorrhage with extension into the ventricle and subarachnoid space
9	Basilar stroke	0.45	Died	Pontine hemorrhage
10	Basilar stroke	0.5	Severe disability	Epistaxis and groin bleeding
11	Basilar stroke	1.25	Moderate disability	Right thalamic hemorrhage with extension into left lateral ventricle and subarachnoid space
12	Basilar stroke	2.0	Died	Intra/retroperitoneal hematoma requiring exploratory surgery
13	Basilar stroke	2.0	Died	Left subdural hematoma requiring evacuation
14	Basilar stroke	2.25	Died	Left temporal and occipital, right cerebellar, and pontine-midbrain-thalamic hemorrhage
15	Basilar stroke	2.5	Died	Pontine and midbrain hemorrhage
16	Basilar stroke	3.0	Died	Pontine and midbrain hemorrhage

ICA = internal carotid artery; MCA = middle cerebral artery; UK = urokinase.

0.03), severe deficits prior to angiography (median GOS = 2 versus 3, $p = 0.03$), higher MAP (median mm Hg 128 versus 112, $p = 0.05$), and higher doses of UK (median U 1.25×10^6 versus 0.5×10^6, $p = 0.004$) (figure 1). Although patients with basilar occlusions were treated with higher median doses of UK (median U 1.13×10^6 versus 0.75×10^6, $p = 0.04$), the association between higher UK dose and SC remained even after stratification by basilar versus nonbasilar occlusion ($p = 0.04$).

Recursive partitioning analysis was performed twice, first using characteristics available before angiography started as well as arterial distribution, function before IA therapy, and MAP (figure 2A), and the second time using the same variables plus UK dose (figure 2B).

Ten of the 16 SC were symptomatic intracerebral hemorrhages (ICH), for a rate of 10/43 (23%). The ICH rate was 5/12 (42%) for patients with basilar occlusion versus 5/31 (16%) for the others. Seven of the 10 patients with symptomatic ICH died in the hospital. Neither pretreatment CT ischemic changes (present in 8 of 34 available scans) nor post-treatment heparin use (in 33 of 43 cases) were associated with SC.

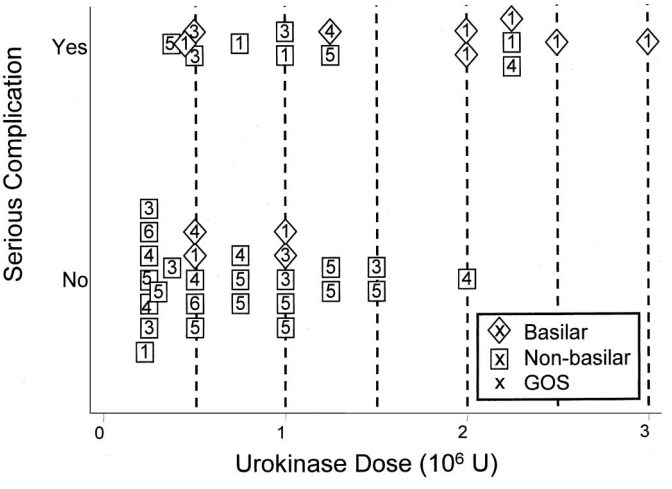
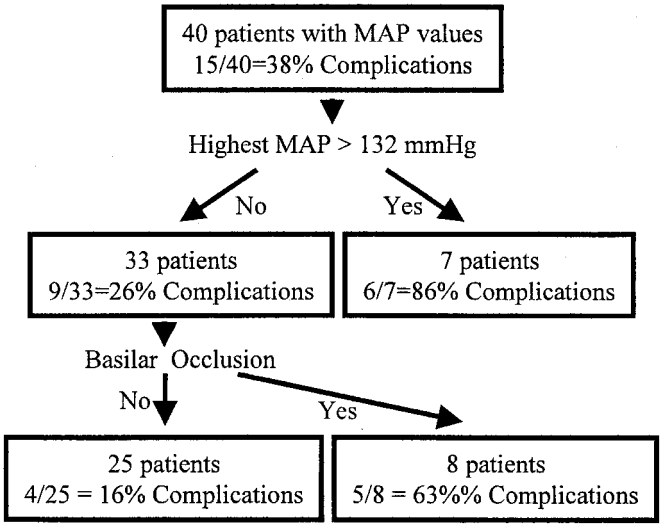


Figure 1. Relationship between intra-arterial dose of urokinase and occurrence of a serious complication of therapy. Within each symbol (nonbasilar [□] and basilar [◇] cases) is the patient's outcome at hospital discharge, as scored by a modification of the Glasgow Outcome Scale: 1 = brain death or death; 2 = brainstem function but not awake (coma); 3 = awake, severe deficits, dependent for activities of daily living (ADL); 4 = awake, moderate deficits, dependent for ADL; 5 = awake, mild deficits, independent for ADL; and 6 = no gross neurologic dysfunction.[1]

Discussion. In this study, more serious complications from IA UK occurred in patients with basilar artery occlusion, severe strokes, higher MAP before treatment, and higher IA UK dose. These findings



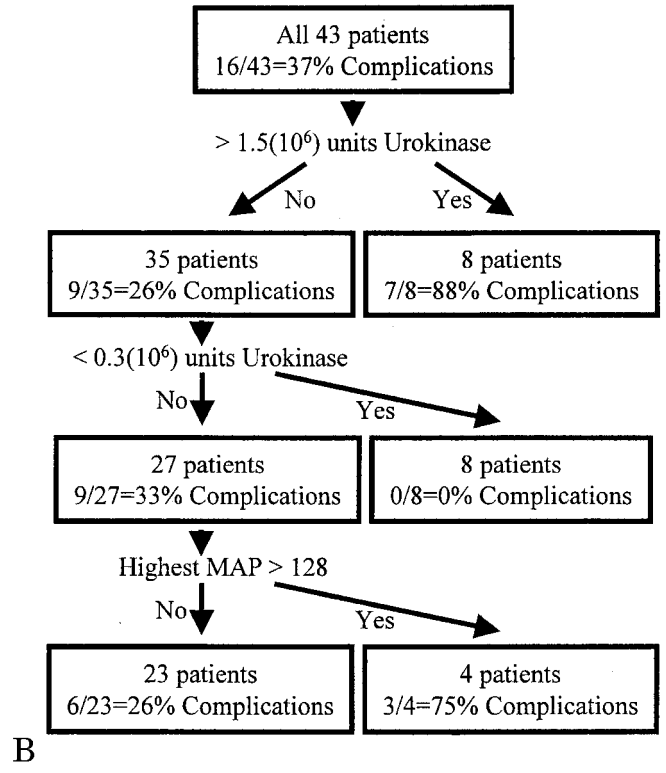


Figure 2. (A) Recursive partition tree identifies patients with serious complications using those variables where $p < 0.1$ *by univariate analysis and available before intra-arterial therapy was started; (B) recursive partition tree identifies patients with serious complications using those variables in part A plus intra-arterial urokinase dose.*

are supported by the literature. In one study, ICH was noted in 4/22 (18%) of cases treated with >0.9 mg/kg of t-PA versus 1/72 (1%) of patients treated with less (exact $p < 0.02$); the five patients who developed hematoma had significantly higher diastolic and mean blood pressures.[3] In another series of 26 patients, the average dose of IA UK in the 10/26 patients found to have ICH on follow-up scans was higher (0.84×10^6 versus 0.59×10^6 U, $p = 0.08$).[4] Higher serum glucose has also been associated with ICH after IA thrombolysis.[5,6]

In December 1999, the PROACT-II randomized trial reported a 15% absolute increase in good outcomes for patients with proximal middle cerebral artery occlusions treated within 6 hours with IA recombinant prourokinase (r-proUK). ICH with neurologic deterioration occurred within 24 hours in 9% (10/108) of thrombolysis patients versus 4% (2/54) of controls ($p = 0.06$).[7] This 9% symptomatic ICH rate is similar to the 16% (5/31) rate in our nonbasilar cases and the 18% (4/22) rate in our patients with MCA disease. Unfortunately, r-proUK may not be approved by the FDA,[8] and UK is no longer manufactured. How well conclusions about one agent can be applied to another is uncertain.[9]

The major limitations of this study are the small number of highly selected patients and the retrospective design. As such, conclusions about which patient characteristics are associated with SC should be interpreted with caution. The small number of patients limits our power to identify significant predictors, and the number of comparisons we performed increases the possibility of finding a spurious association. Also, because UK is no longer manufactured, the inferences based on our findings are less robust and in need of confirmation with the agents currently available.

Only one randomized trial has shown IA thrombolysis for acute ischemic stroke to be an effective therapy. Whether these results translate to other thrombolytic agents and arterial territories is unknown. These issues raise the question of whether IA thrombolysis for acute ischemic stroke should be used outside the clinical trial setting. Our findings and those in the literature argue, at least, for an artery-specific set of protocols enumerating time window, thrombolytic agent, and maximum dose and specifying blood pressure control. Such protocols should undergo institutional review and should involve written informed consent. If clinical information and outcomes could be gathered on a larger cohort of such treated patients, analyses such as those performed in this study might allow for identification of characteristics that would stratify risk of serious complications. This knowledge might allow rational choice of patients for IA thrombolytic treatment, avoiding those with the highest risk of complications, and might also be important in the planning of future clinical trials.

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CME

Drop attacks in older patients secondary to an otologic cause

Article abstract—The clinical features and treatment of seven patients with drop attacks attributable to inner ear disease presenting after age 65 are described. A neurologic or cardiovascular cause of drop attacks was initially suspected. Audiovestibular testing documented a unilateral inner ear disorder. The salient clinical features of these cases are discussed. The patients underwent ablative vestibular surgery, and all compensated well and were free of vertigo and falls up to 10 years postoperatively.

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Drop attacks, that is, sudden falls without loss of consciousness, may account for a significant proportion of potentially dangerous falls in older people. Such attacks are particularly disabling because of the abrupt onset and lack of warning. Sheldon[1] reported that drop attacks accounted for 125 of 500 consecutive falls in older patients. Meissner et al.[2] evaluated the records of 108 patients with drop attacks; 64% were idiopathic. Drop attacks and recurrent vertigo can originate from neurologic conditions such as vertebrobasilar insufficiency, but many neurologists are unaware of the association with inner ear disease. Although Meniere's syndrome is primarily a disease of middle age, patients can present with initial symptoms after age 65. In patients who are older at the onset of vertigo or drop attacks, an otologic cause is oftentimes not suspected. Drop attacks secondary to an otologic cause in the older patient are important to recognize because in intractable cases, vestibular ablative surgery is curative of this dangerous and disabling condition.[3]

Case material. Patients with drop attacks after age 65 attributable to an inner ear pathology who underwent ablative surgery were included. There were 22 patients (6.7% of patients with Meniere's disease over age 65), of whom 7 underwent surgery: 3 men and 4 women with an average age of 72 years. All patients underwent quantitative audiovestibular testing and neurologic examination.

Exemplary case report (Patient 5). A 70-year-old man presented with drop attacks in which he instantaneously collapsed to the ground. He subjectively felt as if pushed to the left. There was no loss of consciousness, no associated focal neurologic symptoms, no warning, and no residual weakness. He had four falls over a 1-year period. He had a 2-year history of recurrent vertigo spells several times a week, lasting 10 minutes to several hours. There was no fluctuation in hearing, ear fullness, or increase in tinnitus associated with the vertigo. Eight years beforehand, he suffered a profound right-sided hearing loss. Neurologic examination and review of systems were negative. Brain MRI with gadolinium, carotid ultrasound, and multiple EEG were normal. A neurologist diagnosed drop attack seizures, but the falls occurred despite phenytoin. At the onset, audiovestibular testing revealed a profound right sensorineural hearing loss (figure) and 100% right caloric paresis. Because he continued to suffer drop attacks despite low-salt diet and diuretics, he underwent right transmastoid labyrinthectomy. By day 2, he was ambulating with a cane; he returned to work within 2 weeks and was able to drive and walk unassisted by 3 weeks. He has had no dysequilibrium, vertigo spells, or drop attacks in 3 years after surgery.

Results. *Summary of clinical characteristics.* Falls. All patients had multiple drop attacks over 9 months to 3 years (see table 1). In all cases, patients reported the subjective sensation of being "pushed," without warning, and no loss of consciousness.

Vertigo spells. All patients reported recurrent episodic vertigo lasting for 10 minutes to 1 day. Patients 2 and 3

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