An Observational Study of Thrombolysis Outcomes in Wake-Up Ischemic Stroke Patients

Dulka Manawadu, MRCP; Shankaranand Bodla, MBBS; Jeff Keep, MRCP; Jozef Jarosz, MRCP, FRCR; Lalit Kalra, PhD

Background and Purpose—Wake-up ischemic stroke (WUIS) patients are not eligible for thrombolysis; the a priori hypothesis was that thrombolysis of selected WUIS patients who meet clinical and imaging criteria for treatment is associated with better outcomes.

Methods—The sample consisted of consecutive WUIS patients who fulfilled predefined criteria: (1) were last seen normal >4.5 hours and <12 hours before presentation; (2) National Institute of Health Stroke Scale score ≥5; (3) No or early ischemic changes <1/3 middle cerebral artery territory on computed tomography imaging; (4) No absolute contraindications to thrombolysis. The primary outcome measure was the modified Rankin Scale of 0 to 2 at 90 days. Other outcome measures were mortality and symptomatic intracerebral hemorrhage.

Results—WUIS patients constituted 10.5% (193/1836) of all stroke admissions. Inclusion criteria were fulfilled by 122 (63%) patients, of whom 68 (56%) were thrombolysed. Thrombolysed and nonthrombolysed patients were comparable for baseline characteristics, but the median baseline National Institute of Health Stroke Scale score was higher in thrombolysed patients (9 versus 11.5; P=0.034). There was no difference in modified Rankin Scale 0 to 2 (25 [37%] versus 14 [26%]; P=0.346), death (10 [15%] versus 14 [26%]; P=0.122), and symptomatic intracerebral hemorrhage (2 versus 0; P=0.204) between thrombolysed and nonthrombolysed patients. After adjusting for age, sex, and baseline National Institute of Health Stroke Scale score thrombolysis was associated with odds ratio of 5.2 (95% confidence interval 1.3–20.3), P=0.017 for modified Rankin Scale 0 to 2 at 90 days and odds ratio of 0.09 (95% confidence interval 1.3–20.3), P=0.003 for death.

Conclusions—Thrombolysis in selected WUIS patients is feasible and may have potential of benefit. (Stroke. 2013;44:XXX-XXX.)

Key Words: acute stroke outcomes stroke management thrombolysis wake-up stroke

People who wake up with symptoms of stroke account for 8% to 27% of ischemic stroke patients but are not thrombolysed because of unknown onset time.1-2 These patients have poorer natural outcomes both with respect to discharge destination and functional outcomes3-4 compared to patients with known time of stroke. Studies show that many patients with wake-up ischemic stroke (WUIS) have clinical and radiological characteristics similar to patients with a known time of stroke onset who receive thrombolytic treatments.1,2,5-7 The a priori hypothesis prior to data collection for this study was that thrombolysis of WUIS patients with clinical and imaging findings of early ischemia will be associated with better outcomes at 90 days.

Methods

The study was undertaken at a tertiary stroke center offering thrombolysis with informed consent to WUIS patients who meet clinical and noncontrast computed tomography (NCCT) imaging eligibility criteria for thrombolysis and would have been treated if presenting within 4.5 hours of stroke onset. Patients were assessed on arrival by stroke fellows using the National Institute of Health Stroke Scale (NIHSS) and NCCT brain images were assessed for early ischemic changes using the Alberta Stroke Program Early Computed Tomography Score.8 Early ischemic changes and hyperdense cerebral arteries were further defined using reconstructed thin slices measuring 1.25 mm.9 Computed tomography perfusion (CTP) imaging was not an obligatory requirement for decision to thrombolysed, but was undertaken immediately after NCCT in 64/122 (52%) of WUIS patients at the request of the treating physician. There were no prespecified mismatch-based criteria for thrombolysis, which remained a clinical decision. Standard dosage schedules for thrombolysis were followed. Patients were managed on the stroke intensive care unit and a follow-up computed tomography (CT) scan was performed at 24 hours. This off-label use of recombinant tissue plasminogen activator (rtPA) with consent is approved by the Novo Procedures and Therapeutics Committee of the Institution.
Results
Of the 1 836 ischemic stroke patients admitted during the study period, 193 (10.5%) had wake-up stroke. Of these, 71 were excluded because (1) last seen normal to presentation exceeded 12 hours (n=36); (2) baseline NIHSS<5 (n=12); (3) last seen normal to presentation <4.5 hours or mild deficits with new symptoms after awakening (n=23). Of the remaining 122 WUIS patients, thrombolysis was undertaken in 68 (56%) patients. Fifty-four (44%) patients were not thrombolysed, being unable to give consent and unaccompanied by relative (n=26), refused to consent (n=9), or treating physician decided against thrombolysis based on no or matched deficits on CTP (n=19).

Table 1 describes the baseline clinical and imaging data for WUIS patients. The thrombolysed group had more women, higher frequency, and higher baseline NIHSS scores. CTP use was more common in thrombolysed patients, 40% of whom showed a perfusion mismatch. Thrombolysed patients were more likely to have atherosclerotic and cardioembolic strokes, and fewer lacunar strokes. Higher proportions of thrombolysed patients survived and showed better functional outcomes.

Table 2. Outcomes Thrombolysed and Nonthrombolysed WUIS Patients With NIHSS Score ≥5

P Value

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Nonthrombolysed (N=54)</th>
<th>Thrombolysed (N=68)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) NIHSS at 24 hours</td>
<td>5 (3,10)</td>
<td>6 (2,13.5)</td>
<td>0.82</td>
</tr>
<tr>
<td>Median (IQR) change in NIHSS at 24 hours</td>
<td>-3 (-4, 0)</td>
<td>-4 (-8, 0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Any ICH (%)</td>
<td>2 (3.7%)</td>
<td>15 (22.1%)</td>
<td>0.004</td>
</tr>
<tr>
<td>sICH (%) by ECASS criteria</td>
<td>0</td>
<td>2 (2.9%)</td>
<td>0.204</td>
</tr>
<tr>
<td>mRS 0 to 1 at 90 days (%)</td>
<td>5 (9.3%)</td>
<td>11 (16.2%)</td>
<td>0.494</td>
</tr>
<tr>
<td>mRS 0 to 2 at 90 days (%)</td>
<td>14 (25.9%)</td>
<td>25 (36.8%)</td>
<td>0.346</td>
</tr>
<tr>
<td>Mortality at 90 days (%)</td>
<td>14 (25.9%)</td>
<td>10 (14.7%)</td>
<td>0.122</td>
</tr>
</tbody>
</table>

ICH indicates intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; sICH, symptomatic intracerebral hemorrhage; and WUIS, wake-up ischemic stroke.
compared with nonthrombolysed WUIS patients, but this was
nonsignificant (Table 2). Any ICH occurred in 12 (22%) of
thrombolysed patients of which 2 (3%) were symptomatic.
Thrombolysis was associated with a nonsignificant shift toward
a better mRS category at 90 days on ordinal regression shift
analysis (Figure 1). Age, baseline NIHSS, and thrombolysis
were independent predictors of mortality and good outcome
(mRS 0–2) at 90 days (Table 3). There were no independent
predictors of sICH. Thrombolysis was associated with a 5-fold
increase in the odds of a good outcome (mRS 0–2) adjusted
for age, sex, and baseline stroke severity.

CTP imaging may have introduced bias favoring better
outcomes to the thrombolysis group. CTP imaging was not
performed if consent to treatment was not available and 19/46
(41%) patients with CTP imaging who showed no or matched
perfusion deficits were not thrombolysed. To exclude this bias,
data were reanalysed for patients in whom NCCT was the
only imaging modality (Table 4). The baseline NIHSS score
was higher in thrombolysed patients (12 versus 9), but they
showed a trend toward lower mortality and better functional
outcomes at 3 months. Baseline NIHSS score was an indepen-
dent predictor of good outcome at 90 days (odds ratio 0.47,
95% confidence interval [CI], 0.26–0.86 per point; P=0.014).
Thrombolysis was associated with odds ratio 6.5 (95% confi-
dence interval, 1.4–24.7; P=0.03) for mRS 0 to 2 at 90 days,
after adjusting for differences in baseline NIHSS score.

### Discussion

Many WUIS patients are not eligible for thrombolytic treat-
ment in routine clinical practice because the time of onset is
not known. Although this observational study did not show a
difference in the primary end point of mRS 0 to 2 at 90 days
between thrombolysed and nonthrombolysed WUIS patients
(37% versus 26%; P=0.35), thrombolysis was an independent
determinant of a better outcome and associated with a 5-fold
odds of achieving an mRS 0 to 2 at 90 days without increas-
ing the risk of hemorrhage, after adjusting for differences in
baseline NIHSS score. This suggests that thrombolytic treat-
ment in selected WUIS patients is feasible with the potential
of benefit over harm.

The outcome of stroke during sleep may be worse compared
with patients with known time of stroke onset, and there is
increasing awareness that selected WUIS patients may be a
reasonable target for intervention. Several studies have shown
that WUIS patients have structural and perfusion CT appear-
cances, diffusion, and perfusion weighted magnetic resonance
(MR) changes, and intracranial large-vessel occlusions similar
to thrombolysed patients with known time of stroke onset.
The effect of recanalization interventions in WUIS patients is
less clear. In a thrombolysis trial using abciximab, 3/21 (14%)
treated WUIS patients had sICH compared with 1/20 patients
receiving placebo, resulting in early cessation of the study.
An observational study comparing 46 WUIS patients (NIHSS
score 16) treated with intravenous or intraarterial rtPA with
34 nontreated WUIS patients (NIHSS score 10.5) showed that
thrombolysed WUIS patients had higher adjusted rates of
good outcomes (odds ratio, 9.2; 95% confidence interval, 1.9–45;
P=0.006). However, only 28 WUIS patients were
treated with intravenous rtPA and outcomes were measured.
at discharge rather than at 90 days. More recently, a pilot randomized controlled study using CT perfusion mismatch as a selection criterion in 12 WUIS patients showed that 4/6 of thrombolysed patients had reperfused with mRS of 0 to 2 at 90 days compared with only 1/5 in the control group.15

This study has systematically assessed outcomes at 90 days with and without thrombolysis in consecutive WUIS patients who would have been eligible for treatment on clinical and imaging criteria, if the time of onset was known. The frequency of sICH (2.9%) in this study compared favorably with the 7.1% in WUS patients treated with intravenous rTPA in a previous study16 and is within the range reported in large registries.18 The proportion of thrombolysed WUIS patients with an excellent or good outcome (16% and 37%, respectively) and mortality (15%) at 90 days were similar to that reported at discharge from hospital previously.14 It is possible that use of multimodal CT or MR imaging of the penumbra may help to select WUIS patients most likely to benefit by thrombolytic treatments and increase the percentage of patients with good outcomes. The role of diffusion/perfusion MR or CT mismatch in patient selection remains equivocal17,18 and is being investigated in ongoing studies. Newer techniques based on MR assessments of lesion age appear promising,19 but need confirmation.

The study is limited by a relatively small sample size and milder strokes in nonthrombolysed patients, which may be the reason why many percentage differences in outcome did not achieve significance. These outcome differences were all consistent in favoring thrombolysis and the association between good outcomes and thrombolysis were confirmed in analyses adjusted for differences in baseline NIHSS scores. Potential bias in sampling was reduced by consecutive sampling of an ongoing registry using predefined inclusion criteria. Bias because of inaccurate or incomplete data were minimized by using standardized definitions, validated scales, and verification against source data. Outcome assessments were performed by trained and certified observers, who were not involved in patient care. Analyses were prespecified and regression models were used to adjust for potential differences in baseline covariates, when assessing outcome. An inadvertent bias favoring treatment may have resulted from patients with less recovery potential not consenting for a high-risk unproven treatment, but only 9 patients refused consent in this study. CTP imaging is another potential source of bias; however, analyses excluding patients undergoing CTP imaging showed a significant independent relationship between thrombolysis and good outcome at 90 days. Finally, the findings reflect practice and outcome at a single center. Although baseline data did not show any statistical difference between the groups, the proportions of some characteristics were not equally distributed and unmeasured bedside bias because of clinical judgment in case selection for thrombolysis remains unknown.

In conclusion, this single-center preliminary study suggests that thrombolysis in WUIS patients selected on defined clinical and imaging criteria is feasible and may be associated with better outcomes. However, the limitations of design emphasize the need for large, multicenter, intervention studies under controlled conditions in these patients.

### Disclosures

The authors have no conflicts of interest to disclose. Dulka Manawadu was involved with the design of the study, data collection, analysis, and writing up the paper. Shankaranand Bodla was responsible for maintaining the database, data extraction, and verification against source data. Jeff Keep contributed to data collection, interpretation of results, and approval of the final version of the paper. Jozef Jarosz contributed to the design of the study, CT image analysis, and interpretation. Lalit Kalra was responsible for the study design, verification of data quality, analysis, interpretation of results, and writing up the paper. Lalit Kalra has access to all the data and takes responsibility for the paper. Sources of Funding

The study was funded by an Institutional Grant from the King’s College Hospital Foundation Trust Research and Development Program.

### Table 4. Baseline Characteristics and Outcomes in With and Without Thrombolysis in WUIS Patients Assessed Using NCCT Alone

<table>
<thead>
<tr>
<th></th>
<th>Nonthrombolysed (N=35)</th>
<th>Thrombolysed (N=23)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age in years</td>
<td>69.8 (16.7)</td>
<td>72.0 (19.4)</td>
<td>0.64</td>
</tr>
<tr>
<td>Men (%)</td>
<td>19 (54%)</td>
<td>8 (35%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>22 (63%)</td>
<td>16 (70%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>10 (29%)</td>
<td>5 (22%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>5 (14%)</td>
<td>4 (17%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Mean (SD) baseline SBP (mm Hg)</td>
<td>156 (27)</td>
<td>157 (26)</td>
<td>0.98</td>
</tr>
<tr>
<td>Mean (SD) baseline DBP (mm Hg)</td>
<td>86 (19)</td>
<td>78 (16)</td>
<td>0.19</td>
</tr>
<tr>
<td>Mean (SD) baseline glucose (mmol/l)</td>
<td>7.7 (3.7)</td>
<td>6.7 (2.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>Median (IQR) baseline NIHSS</td>
<td>9 (5–17)</td>
<td>12 (8–18)</td>
<td>0.34</td>
</tr>
<tr>
<td>Postcirculation</td>
<td>6 (17)</td>
<td>5 (22)</td>
<td>0.67</td>
</tr>
<tr>
<td>ASPECTS 8–10</td>
<td>25 (71)</td>
<td>18 (78)</td>
<td>0.56</td>
</tr>
<tr>
<td>Hyperdense artery sign (%)</td>
<td>10 (29)</td>
<td>9 (39)</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Pathogenicity</strong></td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>Atherosclerotic</td>
<td>21 (10.7%)</td>
<td>5 (15.6%)</td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>74 (37.6%)</td>
<td>13 (40.6%)</td>
<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>30 (15.2%)</td>
<td>2 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Other determined pathogenicity</td>
<td>15 (7.6%)</td>
<td>4 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Mixed/undetermined pathogenicity</td>
<td>57 (29.8%)</td>
<td>8 (25.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (SD) NIHSS at 24 hours</td>
<td>6.5 (4–11.5)</td>
<td>6 (2–18)</td>
<td>0.95</td>
</tr>
<tr>
<td>Median change in NIHSS at 24 hours</td>
<td>−3 (−4–0)</td>
<td>−4 (−8–0.5)</td>
<td>0.47</td>
</tr>
<tr>
<td>Any ICH (%)</td>
<td>1 (2.9%)</td>
<td>4 (17.4%)</td>
<td>0.059</td>
</tr>
<tr>
<td>$s$ICH (%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>mRS 0–1 at 90 days (%)</td>
<td>3 (3%)</td>
<td>3 (13%)</td>
<td>0.34</td>
</tr>
<tr>
<td>mRS 0–2 at 90 days (%)</td>
<td>7 (20%)</td>
<td>7 (30%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Mortality at 90 days (%)</td>
<td>10 (29%)</td>
<td>2 (6%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

ICH indicates intracerebral hemorrhage; $s$ICH, modified Rankin Scale; NCCT, noncontrast computed tomography; NIHSS, National Institute of Health Stroke Scale; $s$ICH, symptomatic intracerebral hemorrhage; and WUIS, wake-up ischemic stroke.
References


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