Wake Up Stroke: Are We Waking Up to a New Era?

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Disclosures:

- Genentech Medical Educational Department (WASSABI)
- Toshiba Stroke Research Center at Buffalo (WASSABI, BUFFALO)
- Honoraria from Elsevier
Introduction:

- Intravenous thrombolysis *IS STILL* the only FDA approved management for stroke (*ONLY 0-3 HOURS*). This is based on the assumption that the rate at which the ischemic process evolves in time is similar in all individuals.

- Patients who develop stroke during sleep as well as aphasic or unconscious patients who develop stroke without a witness being present are *HISTORICALLY* been considered un-illegible for thrombolysis therapy.

- Recent studies have shown that due to significant variability in collateral capacity physiological rather than chronological approach to patient selection for acute stroke interventions is gaining ground.
Pathophysiology:

- Cerebrovascular risk factors for wake up strokes do not differ from non-wake up strokes.

- Lago et al. suggested that circadian hemodynamic changes during sleep leads to decreased CBF which might contribute to the pathogenesis of stroke during sleep.

- OSA is an independent risk factor for stroke. This could happen due to decreased CBF, increased cardiac arrhythmias or increased risk of paradoxical embolism.

- Ozdemir et al. reported that wake up strokes were more common in patients with PFO.
Prevalence And Event Rate:

- Based on multiple retrospective studies it was estimated to be 14-28%.

- Sub-study from the prospective TOAST showed that approximately 25% of all 1272 strokes and TIA were wake up.

- The differences in clinical characteristics between wake up and non-wake up strokes remain unclear.

- In a large population-based study of the Greater Cincinnati/Northern Kentucky region, at least 35.9% of wake up strokes would have been eligible to thrombolysis if arrival time was not a factor.
Early CT Findings:

- Serena et al. found no relevant differences in the clinical, neuroimaging based on NCCT of the brain between wake up strokes and Non-wake up strokes (Retrospective 1248/301).

- Todo et al. suggested that wake up strokes usually develop shortly before awakening (Retrospective 81/17).

- Huisa et al. showed that initial NCCT ASPECTS score was similar between wake up strokes and those with 4 hours of symptoms (Retrospective 867/36).

- Silva et al. showed that the frequencies of CTP mismatch and of large-vessel intracranial occlusions were similar between the two groups (Prospective 676/131).

- Abciximab in Emergency Stroke Treatment Trial-II (AbESTT-II): The frequency of detecting new strokes on NCCT was higher in wake up stroke (39.5% vs. 28.1%).
MRI Findings:

- Fink et al. showed similar lesion volume on DWI/PWI volume and mismatch suggesting that the actual onset may be close to awakening (Retrospective 364/100).

- Thomalla et al. indicated that "mismatch" between positive DWI and negative FLAIR allows the identification of patients that are highly likely to be within the 3-hour time window (Retrospective 120). [50% of 0-3 hours were flair positive]

- PRE-FLAIR: DWI-FLAIR mismatch identified patients within 4.5 h of symptom onset with 62% sensitivity, 78% specificity, 83% PPV, and 54% NPV (multi-center observational 543).

- Conflicting data regarding the association between Flair hyperintensity and increased risk of SICH.
MRI Findings:

- Definition of FLAIR Hyperintensity?
- Is Qualitative visual assessment good enough?
- Is Quantitative assessment practical?
- Does the answer lie under negative Flair or is it a DWI-FLAIR threshold?
- Is any of these measures reproducible in real life?
- Who wakes up first? The patient or the MR technician?
Kucinski et al. Significant univariate predictors of favourable outcome were found to be occlusion type, recanalisation and collateralisation. However, multivariate analysis revealed a significant relationship only between collateralisation and favourable outcome.

More recent work showed that angiographic collateral grade determines the recanalization rate after endovascular revascularization therapy.

When therapeutic revascularization was achieved, beneficial effects were not observed in patients with poor collaterals.

Poor collaterals and recanalization was an independent predictors of both symptomatic and asymptomatic HT.
Past Experience:

- Several empirical trials have attempted to evaluate the safety and efficacy of different therapies in wake up patients.

- Studies investigating the use of MRI or CTP as a selection tool to extend the time window for intravenous thrombolysis have been typically based on visual inspection of the pretreatment imaging revealing a substantial mismatch between irreversibly injured brain and brain that is threatened but still viable.

- Despite its strong foundation, this physiological approach to patient selection has not yet been validated by randomized clinical trials.
DEFUSE is an open-label multicenter study in which acute stroke patients were treated with intravenous tPA between 3 and 6 hours.

The presence of PDM was associated with an increased chance of favorable clinical response after reperfusion (OR, 5.4; P=0.039).

Reperfusion was not associated with a significant increase in the rate of favorable clinical response in patients with CDM (OR, 2.2; P=0.34).
Coregistered mismatch was present in 93% (88/95) compared to 85% (81/95) with standard volumetric mismatch (Prospective 101).

In the coregistered mismatch patients, of whom 45 received alteplase and 43 received placebo, the primary outcome measure of geometric mean infarct growth was significantly attenuated by a ratio of 0.58 with alteplase compared to placebo (1.02 vs 1.77; 95% CI, 0.33–0.99; P=0.0459).
Successful revascularization was achieved in 175 of 237 (73.84%) patients.

Parenchymal hematoma occurred in 21 of 237 (8.86%) patients.

The 90-day mortality rate was 21.5% (51 of 237).

The rate of good outcomes was 45% (100 of 223) in the 223 patients with available modified Rankin Scale data at 90 days or time of hospital discharge.
Forty-six thrombolysed and 34 nonthrombolysed WUS patients were identified.

Two symptomatic intracerebral hemorrhages occurred in treated WUS (4.3%).

Treated WUS had higher rates of excellent (14% vs 6%; P=0.06) and favorable outcome (28% vs 13%; P=0.006), but higher mortality (15% vs 0%) compared to nontreated WUS.

No significant differences in safety and clinical outcomes when compared to non-wake up strokes.
Mean interval between time last-seen well and angiogram was 12.75 hours (median=10).

Symptomatic intracerebral hemorrhage occurred in 3 patients (10%), with 2 being primarily subarachnoid in location.

Total in-hospital mortality including procedural mortality, disease progression, or other comorbidities was 23.3% (n=7).

Overall, mean modified Rankin score at death or last follow-up (mean=10.6 months) was 4.2. At 3 months, total mortality was 33.3% (n=10), 20% had modified Rankin score ≤2, and 33% had modified Rankin score ≤3.
Ongoing Clinical Trials:

- DAWN (MRP/CTP, Endovascular, up to 24 hours, mRS 90 days).
- EXTEND (MRP and DWI<70cc, IV tPA, 3-9 hours, mRS 90 days).
- WAKE UP (CTP, IV tPA, up to 24 hours, SICH).
- AWOKE (MRP/CTP, IV tPA, up to 24 hours, SICH).
- MR WITNESS (DFM, IV tPA, up to 24 hours, SICH).
- WASSABI (CTP, Endovascular vs. IV tPA, up to 24 hours, mRS 90 days).
Wake Up Symptomatic Stroke in Acute Brain Ischemia (WASSABI):

Wake up Symptomatic Stroke - Benefit of Intravenous Clot Busters or Endovascular Intervention (WASSABI)

This study is currently recruiting participants.
Verified March 2012 by Jacobs Neurological Institute

First Received on October 7, 2011. Last Updated on March 29, 2012 History of Changes

Sponsor: Jacobs Neurological Institute
Collaborators: University at Buffalo Neurosurgery Genentech
Information provided by (Responsible Party): Tareq Kass-Hout, Jacobs Neurological Institute
ClinicalTrials.gov Identifier: NCT01455935
Inclusion Criteria:

- Age 18-80
- Unknown time of onset (wake up stroke)
- Last seen normal less than 24 hours before presentation
- Increased time to peak of more than 8 seconds on perfusion maps (tissue at risk to stroke)
- Mismatch greater than 20%
- Large vessel occlusion on CTA (M1, M2, A1, A2, P1, P2, Basilar artery, Vertebral artery)
- ASPCET Score greater than or equal to 7
- NIH greater than or equal to 8
- Other favorable neuroimaging (Per site)
Exclusion Criteria:

- Evidence of intracranial hemorrhage (Intracerebral hematoma, intraventricular hemorrhage, subarachnoid hemorrhage (SAH), epidural hemorrhage, acute or chronic subdural hematoma (SDH)) on the baseline CT
- Historical mRS of ≥2
- NIHSS<8 at the time of treatment
- Positive pregnancy test in women at age of childbearing
- Intracranial or intraspinal surgery within 3 months
- Stroke or serious head injury within 3 months
- History of intracranial hemorrhage
- Uncontrolled hypertension at time of treatment (eg, >185 mm Hg systolic or >110 mm Hg diastolic)
- Seizure at the onset of stroke
- Active internal bleeding
- Intracranial neoplasm
- Arteriovenous malformation or aneurysm
- Clinical presentation suggesting post-MI pericarditis
- INR >1.7
- Administration of heparin within 48 hours preceding the onset of stroke with an elevated aPTT at presentation
- Platelet count <100,000/mm
- Major surgery within 2 weeks
- GI or urinary tract hemorrhage within 3 weeks
- Aggressive treatment required to lower blood pressure
- Glucose level <50 or >400 mg/dL
- Arterial puncture at a noncompressible site or lumbar puncture within 1 week
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### RANDOMIZATION:

<table>
<thead>
<tr>
<th><strong>Group A: Medical Therapy</strong></th>
<th><strong>Group B: Intravenous tPA</strong></th>
<th><strong>Group C: Intra-Arterial Therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Current standard of care per the latest stroke guidelines</td>
<td>- Full dose Iv thrombolysis</td>
<td>- Choice of therapy per experienced Endovascular surgeon and includes:</td>
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<tr>
<td>- Permissive Hypertension up to 220</td>
<td>- 0.9 mg/kg</td>
<td>1. Intra arterial Activase (Maximum dose of 22 mg)</td>
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<tr>
<td>- Antiplatelets therapy: 1. ASA 81 mg PO daily or 2. Plavix 75 mg PO daily or 3. Aggrenox 225mg PO BID</td>
<td>- Maximum dose is 90 mg</td>
<td>2. MERCI device (Maximum of 3 tries, no standard time frame for how long the procedure takes)</td>
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<tr>
<td>- Anti-inflammatory therapy: 1. Lipitor 80 mg PO daily or 2. Crestor 20 mg PO daily</td>
<td>- 10% of the dose will be given over one minute</td>
<td>3. PENUMBRA device (no standard time frame for how long the procedure takes)</td>
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<td>- 90% of the dose will be infused over 1 hour</td>
<td>4. Solitaire AB stent retrieval device.</td>
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<td>- Admission to NICU for 24 hours if no complications</td>
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<td>- Neuro checks every 5 minutes during the infusion</td>
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<td>- Neuro checks every hour after the infusion for 24 hours</td>
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OBJECTIVES:

- Study the safety and the effectiveness of using sophisticated neuroimaging studies as an indicator to treat stroke patients with unknown time of onset

EFFICACY ENDPOINTS

- mRS at 90 days

SECONDARY ENDPOINTS

- NIH 24 hours post treatment.
- NIH on discharge
- mRS at 30 days
- TIMI and TICI pre and post the intervention as an indicator of revascularization rate
<table>
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<th>Study subgroup</th>
<th>Events</th>
<th>C-Reactive Protein (mg/L)</th>
<th>M-H, Fixed 95% CI</th>
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<td>0.9 (1.04; 2.7)</td>
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<td>Odds Ratio (Reanalyzed)</td>
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<td>0.02</td>
<td>0.9 (1.04; 2.7)</td>
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**Total events**

- **Non-reanalyzed**: 70 events
- **Reanalyzed**: 197 events

**Heterogeneity**

- **Non-reanalyzed**: CHI² = 31.81, df = 10, P = 0.001
- **Reanalyzed**: CHI² = 31.81, df = 10, P = 0.001

**Test for overall effect**: Z = 4.24 (P < 0.0001)
<table>
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Note: M-H = Mantel-Haenszel; CI = Confidence Interval; 95% CI = 95% Confidence Interval; Test = Test for overall effect; Z = Z-score; Odds Ratio = Odds Ratio; Favours Recanalized = Favours Recanalized; Favours Non-Recanalized = Favours Non-Recanalized.
SAFETY PLAN:

- **Primary Safety Outcome Measures:**
  - Incidence of symptomatic ICH within 72 hours of intervention defined by ECASSIII as 4 points worsening in NIHSS

- **Secondary Safety Outcome Measures:**
  - Mortality rate at 90 days post stroke

- **Study Termination:** The study will be terminated if 20% of enrolled subjects experience symptomatic intracerebral hemorrhages within the first 36 hours of acute stroke treatment as defined by ECASSIII.

- **DSMB** include 2 neurosurgeons, a neurologist and a statistician. They met after the first 3 patients have been enrolled and every 6 months thereafter.
Why CTP?

- Jovin et al. Recanalization therapy in acute MCA occlusion should ideally be guided by diagnostic methods capable of rapidly and reliably identifying irreversible ischemia.
Does Diffusion-Weighted Imaging Represent the Ischemic Core?

Kranz et al. There was great variability in observed rates of DWI lesion reversal (0%–83%), with a surprisingly high mean rate of DWI lesion reversal (24% of pooled patients). Many studies did not include sufficient data to determine the precise prevalence of DWI lesion growth or reversal.
Reversible Acute Diffusion lesion Already Reperfused (DEFUSE)

- Diffusion reversal rates were significantly increased among cases with favorable clinical response and in patients with early recanalization, especially in regions with normal baseline perfusion.

- Acute ischemic lesions with restricted diffusion are most likely to recover if reperfusion occurs within 6 hours of symptom onset, and reversibility is associated with early recanalization and favorable clinical outcome.
Ischemic diffusion lesion reversal is uncommon and rarely alters perfusion-diffusion mismatch (EPITHET)?

- In 60 patients, apparent reversal involved a median 46% of the baseline DWI lesion and was associated with less severe baseline hypoperfusion.

- Apparent reversal was increased by reperfusion, regardless of the severity of baseline hypoperfusion.

- The median volume of apparent reversal was reduced by 45% when CSF voxels were subtracted.

- Perfusion–diffusion mismatch classification only rarely altered after adjusting the baseline DWI volume for apparent reversal.

- True DWI lesion reversal in only 6 of 93 patients.
Twenty tow patients with acute ischemic stroke in the territory of the middle cerebral artery underwent MRI including DWI, PWI, FLAIR to determine final infarct size, TOF MRA (acute and on day 1 or 2) and a triple echo-T(2)-sequence (calculation of T(2) maps) within 6 h after symptom onset.

There was no significant difference between T(2)-values measured in lesion growth and surviving tissue region of interest for patients with or without recanalization.

Even though it has been shown that T(2)-values increase with time from symptom onset within the infarct core, increased T(2)-values in areas of perfusion impairment do not identify irreversible damaged brain tissue and high T(2)-values are even found in tissue that is not part of the final infarct lesion and can therefore normalize.

T(2)-values are not a valid imaging biomarker in acute stroke to predict tissue outcome??
CT and MR Perfusion Imaging Are Strongly Correlated When Sufficient Brain Volume Is Imaged

- A study of 45 patients with acute middle cerebral artery stroke imaged a mean of 3.8 hours after onset who underwent CT perfusion and MR diffusion (DWI)/perfusion imaging within 3 hours of each other.

- There were significant correlations for **DWI versus CT-cerebral blood volume lesion volumes** ($r^2=0.88$, $P<0.001$), for **MR-MTT versus CT-MTT lesion volumes** ($r^2=0.86$, $P<0.001$), and for **MR-MTT/DWI versus CT-MTT/CT-cerebral blood volume mismatch lesion volumes** ($r^2=0.81$, $P<0.001$).

- MR perfusion and CT perfusion agreed for determining: (1) infarct core < versus $\geq 100$ mL in 41 of 45 (91.1%); (2) MTT lesion size < versus $>2$ cm diameter in 42 of 45 (93.3%); (3) mismatch < versus $>20\%$ in 41 of 45 (91.1%); and (4) inclusion versus exclusion from trial enrollment in 38 of 45 (84.4%) patients.

- Six of 7 disagreements were due to inadequate CT coverage.
CASE 1:

- 65 y/o WF with PMH of Atrial Fibrillation

- Coumadin was stopped for dental surgery

- Presented with severe aphasia and dense right sided hemiplegia (NIH = 16)
**CASE 1:**

- Patient received full dose t-PA

- Discharged home 48 hours later with NIH = 0

- Modified Rankin Scale at 90 days = 0
**CASE 2:**

- 63 y/o AAF with PMH of Atrial Fibrillation
- On Pradaxa last time filled 3 months prior to admission
- Was found unresponsive (NIH = 24)
CASE 2:

- Patient received full dose t-PA
- Discharged home 5 days later with NIH = 0
- Modified Rankin Scale at 90 days = 0
Conclusion:

- It is still a learning curve.
- Encourage recruiting your wake up stroke patients in clinical trials.
THANK YOU!!!