Management of Acute Stroke

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Acute Ischaemic Stroke

Evidence based Treatment: Acute Ischemic Stroke

- Aspirin within 48 hours
- Medical care in the Acute Stroke Unit with multidisciplinary collaboration
- Intravenous thrombolytic therapy (by TPA) within 4.5 hours
- Decompressive hemicraniectomy for malignant MCA infarction

BP Management

- Hypertension occurs commonly after stroke. Even in patients without a history of hypertension, blood pressure is often elevated acutely and typically returns to baseline spontaneously over the first week.
- A U-shaped relationship between admission blood pressure and death has been found in some studies: both elevated and low blood pressures are associated with high rates of early and late death
- Theoretical reasons in favor of lowering elevated blood pressure acutely:
  - reduce the formation of edema
  - lessen the risk of hemorrhagic transformation.
  - allowing blood pressure to remain high risks acute myocardial infarction, pulmonary edema, and renal failure in a population already prone to cardiac and renal disease.

BP Management

- The acute treatment of hypertension is controversial
- Impaired autoregulation in the peri-infarct area will result in further reduction of cerebral blood flow (CBF) with lowering of blood pressure
- Larger blood pressure reductions have been associated with early neurologic worsening, larger infarct volumes, and higher rates of poor outcome and death
- Current consensus: not to control BP unless:
  - SBP > 210, DBP > 120 or MBP > 150
  - Hypertensive urgency: APO, hypertensive encephalopathy, dissection, renal failure
- Preferred antihypertensive medication: IV and short acting for easy and fine titration:
  - Labetolol
  - Nicardipine
  - Esmolol
American Stroke Society 2009 Guidelines

Table 1A. Recommendations for Treatment of Elevated Blood Pressure in Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>High Pressure Limit</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic 120 mm Hg or diastolic 120 mm Hg</td>
<td>Phenylephrine</td>
</tr>
<tr>
<td>Diastolic 120 mm Hg or diastolic 140 mm Hg</td>
<td>Monitor for left ventricular afterload that may not be well compensated for</td>
</tr>
<tr>
<td>Diastolic 140 mm Hg</td>
<td>Norepinephrine/Dopamine</td>
</tr>
</tbody>
</table>

Induced Hypertension

- Rarely needed if head of bed flat, volume is euvoicmic, pressure is not too low.
- Patients with fluctuating neurological deficits that were NOT treated with tPA
- Ensure intravascular volume is optimal prior to inducing hypertension (HTN)
- Treatment of blood pressure sensitive deficits in ischemic stroke that raises systolic BP by 20 to 30% in an attempt to increase cerebral blood flow
  - Usually started in the setting of a low MBP (~80mm Hg) and targeted at a moderate MAP (~110mm Hg)
  - Max systolic BP 200 mm Hg

Induced Hypertension

- Phenylephrine
  - Monitor for left ventricular afterload that may not be well compensated for
- Norepinephrine/Dopamine
  - Monitor for tachycardia
- Abort treatment if no improvement noted
- Risk of induced HTN therapy - reperfusion hemorrhage
- Remains an unproven treatment strategy
- Evidences only from case series: use of induced hypertension in patients who responded with an improvement in neurological exam had improved clinical outcome at discharge

Hyperthermia

- Fever (>37.5°C)
- Correlation was found in a meta-analysis between temperature elevation and cerebral infarct volume
- Increased body temp is a predictor of poorer patient outcome and is an independent factor in short and long-term mortality rate
- Rationale: for additional injury may be related to increased metabolic demands and free radical production

Hyperthermia

- Fever (>37.5°C)
  - Common within the first 48 hours (25%)
  - Warrants workup to identify etiology e.g. infection
  - Initiation of treatment specific to etiology
  - Treatment
    - Treatment of underlying pathology if possible
    - Immediate lowering of temperature
    - Acetaminophen by mouth or rectum: 1gm every 6 hours, as needed (not useful in RCT). Study using 6gm per day is ongoing
    - Ice packs & surface cooling

Body temperature and acute stroke

Acute hyperglycaemia (> 6.1 mmol/l) worsens prognosis of ischaemic stroke

Hyperglycaemia

- Hyperglycaemia is associated with:
  - Infarct expansion & worsening stroke outcomes
  - NINDS analysis found increased risk of hemorrhagic transformation and worse clinical outcome
- Etiology-unknown
  - Lactic acidosis and free radical production
  - Stress induced vs. undiagnosed diabetes
- Goal blood sugar: < 8mmol/l
- Treatment
  - Regular sc insulin or Insulin infusion

Admission glucose in Glucose Insulin Stroke Trial (GIST-UK)

Glucose reduction and outcome in GIST-UK

Medical Treatment of Cerebral Edema

- Use of isotonic solution (normal saline) as maintenance instead hypotonic solution
- Intubation and Hyperventilation
  - Target pCO2 25-30mmHg
  - Transient effect
  - Induce secondary ischaemic injury due to vasoconstriction
  - Use as temporal measures
- Osmotic therapy
  - Mannitol
    - 0.25 to 0.5g/kg IV over 20 minutes q4-6h
    - Some use high dose 1.4g/kg in a bolus in case of sudden deterioration
  - Must avoid hypovolemia and hypotension that can accompany the excessive diuresis.
- Timing and administration of subsequent doses can be guided by clinical response and monitored by the serum osmolality
Medical Treatment of Cerebral Edema

- Osmotic therapy
  - Hypertonic saline
    - Increasing evidence suggests its efficacy may be better than mannitol in acute ischemic stroke without the associated complications of hypovolemia
    - For acute lowering of ICP, 30-60 ml of 23.4% saline is infused over 20 min.
    - 3% hypertonic saline infusions can be used to maintain serum Na gradients
- Moderate Hypothermia
  - 33-34°C
  - External cooling or endovascular cooling

Decompressive Hemicraniectomy

Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials

Inclusion Criteria

| Age 18-60 |
| Clinical deficits suggestive of MCA territory infarct |
| NIHSS > 15 |
| LOC ≥ 1 (not alert, but arousable to minor stimulation) |
| CT > 50% MCA territory infarct or DWI volume > 145 cm³ |
| Onset with 45 hours (Surgery within 48 hours of onset) |
| Written informed consent |

Surgical Procedure

- Large skin incision at the ear
- Bone flap removed
  - Diameter ≥ 12 cm
  - Include frontal, temporal and parietal bones
- Dura opened
- Dural patch secured to enlarge the intradural space

- Temporal muscles and skin flap re-applicated and sutured
- Infracted brain tissue not resected
- Cranioplasty after 6 weeks with stored bone flap or acrylate
Demographics

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Conservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46 +/- 9</td>
<td>44 +/- 9</td>
</tr>
<tr>
<td>History of TIA / Stroke</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Aphasia</td>
<td>55%</td>
<td>60%</td>
</tr>
<tr>
<td>NIHSS</td>
<td>22 (19-25)</td>
<td>22 (21-27)</td>
</tr>
<tr>
<td>Hours to randomization</td>
<td>21.5 (17-29)</td>
<td>20.5 (14-28)</td>
</tr>
</tbody>
</table>

Primary Endpoint

mRS ≥ 5 at 12 months

<table>
<thead>
<tr>
<th>Outcome / Patients</th>
<th>Conservative</th>
<th>Surgery</th>
<th>ARR (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECIMAL DEXTRIN</td>
<td>14 / 10</td>
<td>5 / 29</td>
<td>52.0</td>
<td>25.4-79.5</td>
</tr>
<tr>
<td>BARLET</td>
<td>5 / 16</td>
<td>4 / 17</td>
<td>20.1</td>
<td>9.2-44.5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>20 / 42</td>
<td>13 / 51</td>
<td>32.7</td>
<td>15.9-65.0</td>
</tr>
</tbody>
</table>

Secondary Endpoint

mRS ≥ 4 at 12 months

<table>
<thead>
<tr>
<th>Outcome / Patients</th>
<th>Conservative</th>
<th>Surgery</th>
<th>ARR (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECIMAL DEXTRIN</td>
<td>14 / 16</td>
<td>5 / 29</td>
<td>27.3</td>
<td>14.5-48.1</td>
</tr>
<tr>
<td>BARLET</td>
<td>5 / 10</td>
<td>4 / 14</td>
<td>17.5</td>
<td>5.9-40.5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>20 / 41</td>
<td>19 / 51</td>
<td>16.7</td>
<td>6.4-40.8</td>
</tr>
</tbody>
</table>

Death at 12 months

<table>
<thead>
<tr>
<th>Outcome / Patients</th>
<th>Conservative</th>
<th>Surgery</th>
<th>ARR (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECIMAL DEXTRIN</td>
<td>14 / 15</td>
<td>5 / 29</td>
<td>23.0</td>
<td>13.3-40.4</td>
</tr>
<tr>
<td>BARLET</td>
<td>5 / 12</td>
<td>4 / 14</td>
<td>15.6</td>
<td>5.4-39.8</td>
</tr>
<tr>
<td>TOTAL</td>
<td>20 / 41</td>
<td>19 / 51</td>
<td>17.0</td>
<td>6.0-40.1</td>
</tr>
</tbody>
</table>

Discussion

- It is a pooled analysis of three RCT
- Decompressive surgery increased survival from 28% to 78% and the probability of survival with mRS≤3 doubles
- The probability of survival in a condition requiring assistance from others (mRS 4) increases > 10 times
- The results can probably not be generalized to patients ≥60 yr old, but RCT is still ongoing for elderly population
Evidence of IV TPA Treatment within 3hrs

National Institute of Neurological Disorder and Stroke (NINDS) trial
- double blinded randomized control trial
- 624 patients
- TPA - dose: 0.9 mg/kg
  window: 3 hrs
- early infarct signs in CT scan is NOT an exclusion criteria
- Target BP control:
  Protocol using IV Labetalol and/or IV Nitroprusside to maintain BP ≤ 180/105
  NEJM 1995;333:1581-1587

NINDS - Results
- As compared with patients given placebo, patients treated with TPA were at least 30% more likely to have minimal or no disability at 3 months, as measured by the outcome scale
- Absolute increase in favourable outcome: 11 to 13%
- Number needed to treat (NNT): 8
- Overall symptomatic hemorrhages 6.4%, compared with 0.6% for placebo

Research result reproduced in clinical setting and community hospitals

More patients recover with minimal or no disability with Activase® (t-PA)

<table>
<thead>
<tr>
<th>NINDS results at 3 months*</th>
<th>Pooled randomised controlled trials*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NIH Stroke Scale</strong></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>23%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>24%</td>
</tr>
<tr>
<td>Stable</td>
<td>23%</td>
</tr>
<tr>
<td><strong>Rankin Index</strong></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>22%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>23%</td>
</tr>
<tr>
<td>Stable</td>
<td>22%</td>
</tr>
<tr>
<td><strong>Modified Rankin</strong></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>22%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>23%</td>
</tr>
<tr>
<td>Stable</td>
<td>22%</td>
</tr>
<tr>
<td><strong>Glasdeg outcome</strong></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>22%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>23%</td>
</tr>
<tr>
<td>Stable</td>
<td>22%</td>
</tr>
</tbody>
</table>

Notes: NIH = National Institutes of Health. Rankin scale 0 = normal health, 1 = mild disability, 2 = moderate disability, 3 = severe disability, 4 = bed bound, 5 = dead.

Research result reproduced in clinical setting and community hospitals

Outcomes of SITS-MOST compared to randomised controlled trials

Outcomes for new and experienced centres in SITS-MOST compared with RCTs

<table>
<thead>
<tr>
<th></th>
<th>SITS-MOST</th>
<th>Randomised controlled trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>SICH rates per</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SITS-MOST new</td>
<td>1.6% (81/4958; 1.2–2.0)</td>
<td>1.3–2.0</td>
</tr>
<tr>
<td>SICH rates per</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SITS-MOST experienced</td>
<td>1.7% (26/1486; 1.2–2.6)</td>
<td>1.2–2.6</td>
</tr>
<tr>
<td>SICH rates per</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NINDS/Cochrane†</td>
<td>7.3% (359/4947; 6.6–8.0)</td>
<td>6.6–8.0</td>
</tr>
<tr>
<td>SICH rates per</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NINDS/Cochrane‡</td>
<td>7.3% (109/1491; 6.1–8.7)</td>
<td>6.1–8.7</td>
</tr>
<tr>
<td>SICH rates per</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NINDS/Cochrane‡</td>
<td>8.6% (40/465; 6.3–11.6)</td>
<td>6.3–11.6</td>
</tr>
<tr>
<td>Mortality within</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>10.6% (505/4742; 9.8–11.6)</td>
<td>9.8–11.6</td>
</tr>
<tr>
<td>Independence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(modified Rankin Score, 0–2) at 3 months</td>
<td>54.4% (2544/4675; 53.0–55.8)</td>
<td>53.0–55.8</td>
</tr>
</tbody>
</table>

The results suggest a potential benefit up to 4.5hr, but this potential might come with some risks.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active (tPA)</td>
<td>3.4 (1.7–6.5)</td>
</tr>
<tr>
<td>Low (tPA)</td>
<td>1.0 (0.9–1.2)</td>
</tr>
</tbody>
</table>

Evidence of IV TPA Treatment from 3 to 4.5hr

The results suggest a potential benefit up to 4.5hr, but this potential might come with some risks.
The odds The odds for a favorable outcome (the ability to return to an independent lifestyle) after stroke were 28% higher with alteplase than with placebo.

Management after IV rTPA given

Monitoring of patient after rTPA Rx

- Close observation is necessary for the first 24 hours
- Every 15 minutes for 2 hours
- Every 30 minutes for 4 hours
- Then hourly observation
- Neuroobservation and BP monitoring
- Sleeping patient must be waken up to confirm the conscious level
- Aim to detect any neurological deterioration and keep BP < 150/105

Further Care of Patient

- Minimise physical handling of patient
- Strict bed rest for the first 24 hours
- Safety precautions to prevent fall
- Minimise invasive procedures
- Avoid foley insertion for at least 30 minutes after infusion
- Avoid Ryle tube insertion for at least 24 hours
- Leave heparin block in situ for blood taking if possible
- If venepuncture is required, apply direct pressure to puncture site for 20 minutes
Key Observations

- Neurological deterioration
- Decreased GCS
- Increased weakness
- Symptoms suspicious of ICH
  - Sudden headache
  - Sudden vomiting/nausea
  - Sudden surge of BP
- Systemic bleeding
- Allergic reaction

Perform CT brain as soon as possible if ICH is suspected

Also prepare to give 6 unit of platelet conc and 6 unit of cryoprecipitate/FFP

Symptomatic ICH after IV TPA Treatment

- No anti-dose
- Adequate replacement of Clotting factors and Platelet Concentrate
- Intubation and hyperventilation
- Neurosurgeon assessment

Table 1: Risk of symptomatic intracranial hemorrhage related to administration of tissue plasminogen activator in the NINDS Stroke Study

<table>
<thead>
<tr>
<th>Pretreatment variable</th>
<th>Risk of symptomatic intracranial hemorrhage, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS score</td>
<td></td>
</tr>
<tr>
<td>&gt; 20 (most severe)</td>
<td>17</td>
</tr>
<tr>
<td>11–20</td>
<td>4–5</td>
</tr>
<tr>
<td>&lt; 10 (least severe)</td>
<td>2–3</td>
</tr>
<tr>
<td>Edema or mass effect on CT</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>31</td>
</tr>
<tr>
<td>Absent</td>
<td>6</td>
</tr>
</tbody>
</table>

Summary

- Time is brain, act fast to deliver the drug.
- Main risk of treatment is ICH
- Tight BP control < 180/105 is important to reduce the complication of ICH
  - If the BP is not high initially, it is not common to have sudden surge up of hypertension. Such occurrence might be suggestive of developing ICH
- Observe for any neurological deterioration to consider repeated CT scan study
Intracerebral Haemorrhage

**BP Management**

- **BP reduction**
  - **Potential benefits:**
    - May ameliorate local edema
    - May limit early haematoma growth
  - **Potential risk:**
    - Aggravation of perilesional ischemia

**INTERACT study**

- Randomized, open-label, active-control, parallel-assignment, safety/efficacy study
- Randomized to aggressive BP management, with a goal of reducing systolic BP to less than 140 mm Hg within 1 hour, or standard management targeting systolic BP less than 180 mm Hg
- Mean time from symptom onset to treatment was around 4 hrs
- At 1 hour the mean systolic BP was 153 mm Hg in the intensive group and 167 mm Hg in the control group
- From 1 to 24 hours, BP was 146 mm Hg in the intensive group and 157 mm Hg in the control group
- Mean proportional hematoma growth in the intensive group was 13.7% compared with 36.3% in the control group (difference 22.6%, 95% CI, 0.6-44.5%; P=0.04) at 24 hours
- Intensive BP lowering treatment did not alter the risks of neurologic deterioration or secondary clinical outcomes at 90 days

**ICH PET Study: no evidence of peri-haematoma ischeamia**

**Practical Recommendation**

- To maintain a systolic BP < 180 mm Hg and/or mean BP < 130 mm Hg
- Reduction in mean arterial BP by 15% within the first 24 hrs is probably safe
- IV labetalol and nicardipine is the preferred drug for emergency use
- No solid data to support more aggressive BP control to arrive at a better clinical outcome

**American Stroke ICH Guideline 2007**

**TABLE 2. Suggested Recommended Guidelines for Treating Elevated Blood Pressure in Spontaneous ICH**

1. If SBP is >180 mm Hg or MAP is >130 mm Hg, then consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 5 minutes.
2. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is evidence of or suspicion of elevated ICP, then consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications to keep central perfusion pressure >60 to 80 mm Hg.
3. If SBP is >180 mm Hg or MAP is >130 mm Hg and there is not evidence of or suspicion of elevated ICP, then consider a modest reduction of blood pressure via MAP of 110 mm Hg or target blood pressure of 160/90 mm Hg using intermittent or continuous intravenous medications to control blood pressure, and clinically reexamine the patient every 15 minutes.

SBP indicates systolic blood pressure; MAP, mean arterial pressure.
Seizure Prophylaxis

- Seizure after ICH
  - 10% have generalized tonic-clonic seizures
  - No evidence of prevention of epileptogenesis with anticonvulsant
- Option: prophylactic phenytoin for 7 days for patients with large ICH at risk for increased ICH or patients with intracranial surgery done

Surgical Trial of ICH

Early surgery versus initial conservative treatment
(STICH Trial)
- 1033 primary ICH patients
- ICH onset within 72 hrs
- Favorable outcome at months
  - Early surgery: 26%
  - Initial conservative: 24%
  (p=0.414)

Patients could be included if the responsible neurosurgeons was uncertain about the benefits of either Rx (the clinical uncertainty principle)
- Early surgery group: time between onset and surgery = 30 hr (median), 16% done within 12 hrs.
- Initial conservative Rx group: 26% underwent surgery after an initial period of observation.

Surgical Trial of ICH

Acute Haemostatic Treatment

FAST Study - Phase II dose-finding study
Recombinant Activated Factor VII (rFVIIa) in Acute ICH study
- 399 primary ICH patients
- Treatment given within 4 hours of ICH onset
- Randomized controlled trial
- Randomized to placebo and three different dosage of rFVIIa
- Primary outcome: % change in ICH volume at 24 hrs
- Clinical outcome: functional score at 90 days

<table>
<thead>
<tr>
<th></th>
<th>Early surgery (n=503)</th>
<th>Initial conservative treatment (n=330)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of Haematoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>196 (39%)</td>
<td>214 (40%)</td>
</tr>
<tr>
<td>Basal ganglia/thalamic</td>
<td>210 (42%)</td>
<td>224 (42%)</td>
</tr>
<tr>
<td>Both</td>
<td>94 (19%)</td>
<td>90 (17%)</td>
</tr>
<tr>
<td>Not assessable</td>
<td>3 (1%)</td>
<td>2</td>
</tr>
<tr>
<td>Left side of haematoma</td>
<td>265 (53%)</td>
<td>285 (54%)</td>
</tr>
<tr>
<td>Haematoma volume (mL)*</td>
<td>40 (24–63)</td>
<td>37 (23–60)</td>
</tr>
<tr>
<td>Minimum depth from cortical surface (cm)</td>
<td>1.0 (0.1–2.0)</td>
<td>1.0 (0.6–2.0)</td>
</tr>
</tbody>
</table>

Data are number (% or median (IQR). *Volume= length×width×height/2."
Efficacy and Safety of Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage

Stephan A. Mayer, M.D., Nikolai C. Brun, M.D., Ph.D., Kamilla Bagtrup, M.Sc., Joseph Broderick, M.D., Stephen Davis, M.D., Michael N. Diringer, M.D., Brett E. Skolnick, Ph.D., Thorsten Steiner, M.D., for the FAST Trial Investigators

N Engl J Med
Volume 358(20):2127-2137
May 15, 2008

FAST II Study – Phase III Study

N Engl J Med
Volume 358(20):2127-2137
May 15, 2008

Table 1: Baseline Volumes on CT According to Study Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=66)</th>
<th>rtVIIa 40 μg (n=63)</th>
<th>rtVIIa 80 μg (n=67)</th>
<th>Combined (n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage volume, ml</td>
<td>31.4 (22.9)</td>
<td>30.2 (22.7)</td>
<td>31.9 (22.6)</td>
<td>31.5 (22.8)</td>
</tr>
<tr>
<td>Hemorrhage volume, % of brain volume</td>
<td>6.2 (4.3)</td>
<td>6.4 (4.4)</td>
<td>6.3 (4.4)</td>
<td>6.3 (4.4)</td>
</tr>
</tbody>
</table>

Kaplan-Meier Survival Curves

Table 2: Clinical Outcomes and Therapeutic Efficacy in Subsets of Patients at All Eases According to Study Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=66)</th>
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<th>Combined (n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>38 (59)</td>
<td>33 (52)</td>
<td>34 (53)</td>
<td>34 (53)</td>
</tr>
<tr>
<td>rtVIIa 40 μg (n=63)</td>
<td>32 (51)</td>
<td>31 (50)</td>
<td>31 (50)</td>
<td></td>
</tr>
<tr>
<td>rtVIIa 80 μg (n=67)</td>
<td>35 (55)</td>
<td>35 (55)</td>
<td>35 (55)</td>
<td></td>
</tr>
<tr>
<td>Combined (n=196)</td>
<td>35 (55)</td>
<td>35 (55)</td>
<td>35 (55)</td>
<td></td>
</tr>
</tbody>
</table>

*Median values are shown. rtVIIa, recombinant activated factor VIIa; *p* ≤ 0.05 compared to placebo.
Clinical Outcome at 90 Days According to the Modified Rankin Scale

Conclusion of FAST II Study
Hemostatic therapy with rFVIIa reduced growth of the hematoma but did not improve survival or functional outcome after intracerebral hemorrhage

Management of Warfarin related ICH

Hematoma Growth in Oral Anticoagulant Related Intracerebral Hemorrhage

Vitamin K
- Usually 10mg iv, Take 6-24 h to correct the INR
- Replacement of factors IX and X might take >24 hours
- To sustain the reversal of the warfarin effect. Replacement of clotting factors by FFP alone is not long lasting
- Risk of anaphylaxis with intravenous injection (very rare)
- Warfarin resistance in higher doses up to 1 wk

FFP Infusion
- Replacement of all clotting factors
- Requires checking for ABO blood compatibility
- With prior type & screen, take 0.5 hr for unfrozen procedure in blood bank, 1 hr for infusion (Total: 1.5 hr)
- Without prior type & screen, take 2 hr for cross match, 0.5 hr for unfrozen procedure in blood bank, 1 hr for infusion (Total: 3.5 hr)
- Usual dosage: 15 ml/kg infusion
- 1 to 2 hr for infusion, typical 12-32 h for reversal
- Rapid infusion of large volume of FFP might cause fluid overload
**Case example**

- F/57
- Transferred from UCH with warfarin related ICH to NS unit
- On arrival GCS 14
- Vit K not given, 6 unit FFP ordered
- Deteriorated to GCS 11 (40 minutes later)
- Deteriorated to GCS 7 (60 minutes later)
- FFP still not yet started. FFP started 2.5 hr later
- Patient died

**Implication**

- Half of the patients with warfarin related ICH will deteriorate, most within 6 hrs. due to ICH expansion
- FFP was not fast enough to reverse the bleeding tendency
- Any other treatment?

Warfarin inhibit the vitamin K action to produce Factor II, VII, IX and X
Prothrombin Complex Concentrate (PCC)

- It contains factor II, IX, X +/- VII
- Previously widely used in the treatment of hemophilia B prior to the availability of high-purity plasma-derived and recombinant Factor IX concentrates
- Have been commonly used to treat warfarin-associated ICH in Europe
- Commercial products in powder for reconstitution (not a blood product from Blood Bank)

Studies comparing PCCs with FFP

- Fredriksson et al: retrospective review
  - comparing PCC (average dose 25.8 U/kg) with FFP (average 600ml) in 17 patients with ICH
  - PCC was associated with a significantly shorter time to INR correction (P < 0.001)
  - PCC significantly reduced the progression of ICH signs and symptoms compared with FFP (P < 0.005)

- Makris et al: retrospective review
  - comparing the efficacy of PCC injection or FFP infusion in 41 patients with major bleeding or who required urgent reversal of warfarin therapy
  - Complete correction of the INR occurred within 15 min in 28 of 29 patients treated with PCC (50 U/kg) versus none of 12 patients given FFP (800ml)

Conclusions of the Review

- While PCCs offer rapid and specific replacement of the depleted vitamin K-dependent factors, there is a pressing need for further evidence-based treatment guidelines to optimize therapy
- Until such trials are accomplished, accumulating experience demonstrates that PCCs are superior to FFP for the urgent reversal of warfarin in patients with life-threatening hemorrhage, especially in patients with profound suppression of vitamin K-dependent factors

Recombinant FVIIa (NovoSeven)

- At pharmacologic doses, recombinant activated factor VII (rFVIIa) directly activates factor X on the surface of activated platelets, resulting in a thrombin burst and acceleration of coagulation
- Bolus injection, reversal of INR within 15 minutes
- Short half-life, very expensive
- Potentially prothrombotic, uncertain safety?
NovoSeven® Mode of Action

Tissue factor (TF)/FVIIa, or TF/rFVIIa interaction, is necessary to initiate haemostasis.

At pharmacological concentrations rFVIIa directly activates FX on the surface of locally activated platelets. This activation initiates the "thrombin burst", independently of FIX.

This step is independent of TF.

The thrombin burst leads to the formation of a stable clot.

Recombinant Factor VIIa for Rapid Reversal of Warfarin Anticoagulation in Acute Intracranial Hemorrhage

- A consecutive series of 7 patients (median age, 87 years; 5 women) with symptomatic, nontraumatic warfarin-related ICH treated with intravenous rFVIIa
- Mean INR decreased from 2.7 to 1.08 after administration of rFVIIa
- The median Glasgow Coma Scale was 14 (range, 4-15).
- The mean time from onset to treatment was 6.2 hours.
- The mean initial dose of rFVIIa was 62.1 µg/kg.
- Five of the 7 patients survived and were dismissed from the hospital with significant disability (Glasgow Outcome Scale, 3)
- 2 patients died during hospitalization

Pre Rx | Post Rx


- 13 publications with 1–16 patients included in each
- All publications were retrospective, nonrandomised and consisted largely of case series or case reports without adequate controls
- Most patients also received FFP as well as vitamin K in addition to the rFVIIa.
- Authors' conclusion: although the rFVIIa rapidly corrects the INR, its clinical impact on stopping bleeding was unclear

Adverse Effect of PCC and rFVIIa- Prothrombotic Effect

- The main adverse effect of concern with both PCC and rFVIIa is the risk of thrombosis when given to reverse the anticoagulation of individuals at high pro-thrombotic risk in the first place
- Leissinger et al: systematic review of 14 clinical trials on the role of PCC in warfarin reversal
- 7 (1.5%) thrombotic events (3 thrombotic strokes, 2DVTs and 2 non-Q-wave MIs) reported in a total of 460 patients
Adverse Effect of PCC and rFVIIa- Prothrombotic Effect

- Insufficient patients on warfarin treated with rFVIIa to be able to evaluate the thrombotic risk in this specific situation.
- Hsia et al: recent meta-analysis of 22 randomised controlled trials of rFVIIa in non-hemophilic patients
- the thrombotic risk was higher for arterial events in the rFVIIa-treated patients at 4.5% compared to the placebo group 2.0%

What is the standard Rx for acute reversal of warfarin effect?

- Vit K 10mg IV is a must
- Together with FFP or PCC or rFVIIa or any combination of them?
- No high level clinical outcome based evidence to support


Recommendation
- Reversal of anticoagulation in patients with major bleeding requires administration of a factor concentrate (50U/kg) in preference to FFP (15ml/kg), when this is available (grade B, level III)
- administration of intravenous (5 or 10mg) rather than oral vitamin K (grade B, level IIa)

In patients with life-threatening bleeding (eg, intracranial hemorrhage) and elevated INR, regardless of the magnitude of the elevation, we recommend holding warfarin therapy and administering fresh frozen plasma, PCC, or recombinant factor VIII supplemented with vitamin K (10mg) by slow IV infusion; repeated, if necessary, depending on the INR (Grade 1C)
To reverse the effects of warfarin, vitamin K1 can be given. Immediate reversal is achieved with a prothrombin complex concentrate (PCC) and fresh frozen plasma (FFP). Vitamin K1 is essential for sustaining the reversal achieved by PCC and FFP. Prothrombinex-HT is the only PCC approved in Australia and New Zealand for warfarin reversal. (25-50 U/kg) It contains factors II, IX and X, and low levels of factor VII. FFP (150-300ml) should be added to Prothrombinex-HT as a source of factor VII when used for warfarin reversal.

Conclusion: Warfarin Related ICH

- Warfarin related ICH is a life threatening disease.
- Immediate reversal of warfarin effect is essential.
- Vit K 10mg is a must to sustain the effect of warfarin reversal.
- FFP + Vit K is not effective to prevent the deterioration.
- PCC seems faster than FFP. But the optimal dosage is not yet well defined.
- The thrombotic risk is low (1 to 2%) as compared with the ICH expansion risk (50%).
- rFVIIa seems to be a promising treatment option to arrest the ongoing bleeding.
- In view of the prothrombotic effect of PCC, it is only used for acute reverse of warfarin effect in situation of life threatening bleeding only.

Thank You