Emerging therapies for Intracerebral Hemorrhage

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Learning objectives

Update on emerging trends in ICH for

- Blood pressure management
- Anticoagulation reversal
- Surgical advances
Patient KK

✓ 80 year old male
✓ Very active, independent.
✓ Well controlled hypertension, hyperlipidemia, remote smoking, social EtOH.
✓ Collapsed in the bathroom, not moving left side, awake, dysarthric, right gaze preference, left hemiplegia, neglect, following commands.
110 cc right basal ganglia ICH with IVH.
Audience question 1

Which of Mr. KK’s risk factors put him at risk for the ICH?

- High cholesterol
- High blood pressure
- High blood sugar
- Smoking
Risk factors for primary ICH

1. Older age
2. Hypertension
3. ETOH abuse
4. Prior ICH
5. Anticoagulation
6. Carriers of apolipoprotein ε 2 or ε 4 allele
Types of spontaneous (i.e. non-traumatic) Intracerebral Hemorrhage

• Primary (80-90%)
  – Hypertension
  – Cerebral amyloid angiopathy

• Secondary
‘Tis a rare thing….But

85% Ischemic

15% Hemorrhagic

Brain / Subarachnoid

25% Large Vessel Atherosclerosis

20% Embolism from Heart

30% Undetermined

20% Small Vessel Atherosclerosis

5% Unusual Causes

15% Embolism from Heart

5% Unusual Causes

20% Hemorrhagic

30% Undetermined
ICH remains a devastating stroke.

Only ~ 20% are fully independent at 6 months.

Mortality: 6 months, 30-50%.

ICH score and mortality at 1 month

**Patient KK’s ICH score = 3**
Functional outcome at 90 days

FUNC Score Prediction Tool

<table>
<thead>
<tr>
<th>FUNC Score</th>
<th>[0-4]</th>
<th>[5-7]</th>
<th>[8]</th>
<th>[9-10]</th>
<th>[11]</th>
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<tbody>
<tr>
<td>Entire Cohort</td>
<td>0</td>
<td>13</td>
<td>42</td>
<td>66</td>
<td>82</td>
</tr>
<tr>
<td>Survivors Only</td>
<td>0</td>
<td>29</td>
<td>48</td>
<td>75</td>
<td>95</td>
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% functionally independent at 90 days
Dilemma

- With a predicted 70% mortality at 1 month and 0% chance of functional recovery, in this 80 year old male, what should I advise him and his family?

- Oh, BTW, his daughter is an ICU nurse at my hospital.
SELF FULFILLING PROPHECY

We become what people expect us to become

…and so a negative belief predicts a negative behaviour
If a teacher thinks you will fail in an exam you probably will!
The self fulfilling prophecy in ICH

• Current methods of prognostication in individual patients early after ICH are likely biased by failure to account for the influence of withdrawal of support and early DNR orders.

• Aggressive full care early after ICH onset and postponement of new DNR orders until at least the second full day of hospitalization is probably recommended.
How I view ICH related outcome

- Excellent medical care has a potent, direct impact on ICH morbidity and mortality, even before a specific therapy is found.

- In many cases, it is the aggressiveness of clinical care that determines the direct mortality from the disease.
ICH outcomes are improved in a neuroICU

• Initial monitoring and management of ICH patients should take place in an intensive care unit with physician and nursing neuroscience intensive care expertise. Class 1 recommendation.

AHA ICH guidelines, Stroke 2010
Can we and if so, how to change ICH outcome?

Only ~ 20% are fully independent at 6 months

Mortality: 6 months, 30-50%
THERAPEUTIC TARGETS IN ICH

- Blood Pressure Control
- Hemostatic Therapies
- Clot Removal
- Anti-Inflammatory Therapies

- Hematoma Expansion
- Mass Effect from Hematoma & Edema
Emergency ICH management
Principles

- Stop ongoing bleeding
- Prevent hematoma expansion
- Accelerate removal of blood from the brain
Emergency ICH management Principles

- Stop ongoing bleeding
- Prevent hematoma expansion
Strategies to limit ICH expansion.

- Reducing the driving force (i.e. Blood pressure).
- Treating the compromised coagulation.
BP lowering after ICH: Competing interests
Hematoma expansion Vs penumbra

↓ Hematoma Expansion

3h

6h

↓ Cerebral Blood Flow
Audience question 2

- The optimal systolic blood pressure goal for blood pressure lowering in the first day after ICH is
  - 180 mm Hg
  - 160 mm Hg
  - 140 mm Hg
My approach to BP lowering in ICH  
*(in 2013)*

- **For small ICH (< 25 cc)** - BP lowering to SBP < 140 mm Hg seems reasonably safe. (*Interact 2 study*)

- **For larger ICH** - I lower to SBP < 160 mm Hg or MAP of < 110 mm Hg (*AHA guideline, Class 2b*)

- In young normotensives, coagulopathy, vascular lesion- < 140 mm Hg is reasonable.

- **ATACH-2**: NIH funded, Phase 3, RCT, iv nicardipine, < 140 Vs 140-180 mm Hg.
Emergency ICH management
Principles

- Stop ongoing bleeding
- Prevent hematoma expansion
76yo M, ICH, INR=5.5

Non-Con CT @ 60 mins post sx onset

R pupil becomes fixed in ED, follow-up CT 140 mins later shows interval expansion
Audience response question # 3

Which of the following is the best strategy for emergency warfarin reversal?

A. Subcutaneous Vit K + FFP
B. Intravenous Vit K + FFP
C. Intravenous Vit K + Profilnine (3F- PCC)
D. Intravenous Vit K + Kcentra (4F-PCC)
Novoseven*

VIIa

Warfarin

Rivaroxaban
Apixiban

Plasma

VIIa, Xa, IIa, Ia

Vla

IIa

Va

Plasmin

Platelet transfusion

Antiplatelet agents

Adapted from: Dr. Jean-Marc Olivot
Stanford emergency warfarin reversal protocol

**INR 1.2-1.5**
- Vit K 5 mg IV
- Liquid Plasma 1-2 units
- Recheck INR in 15-30
  - INR ≤1.2
    - FFP 1 unit
    - INR q6 till 2 readings ≤1.2
  - INR > 1.2
    - Vit K 5 mg
    - Recheck INR in 15-30

**INR ≥1.6**
- Vit K 10 mg IV
- Liquid Plasma 2-3 units
- Recheck INR after Plasma infusion
  - INR ≤4
    - Profilnine 25 units/kg
  - INR > 4
    - Profilnine 35-50 units/kg
- INR ≥1.6
- INR > 1.2
  - FFP 2 units+/- PCC repeat if > 6 hrs.
  - Recheck INR after Plasma infusion
    - INR ≤1.2
    - INR q6 till 2 readings ≤1.2
    - Recheck INR after Plasma infusion
      - INR ≥1.6
      - INR > 1.2
      - FFP 2 units+/- PCC repeat if > 6 hrs.
Does the protocol work?

80 year old woman with INR 18.9.

The warfarin reversal protocol was implemented, INR 1.1 reached within 2 hours. She has since returned home with minimal deficits.
FDA approves Kcentra- 4 factor PCC, 4/2013

- 4F PCC- 2, 7, 9, 10, protein C & S
- Kcentra + Vitamin K Vs FFP + Vitamin K (n=212)
  - INR < 1.3 at 30 minutes in 63% Vs 9%
  - 87% less volume (~ 100 cc Vs 900 cc)
  - 7 fold faster infusion time (24 min Vs 3 hrs)

Stanford emergency warfarin reversal protocol

**INR < 2**
- Vit K 5 to 10 mg IV
- Liquid Plasma 1-2 units

**INR 2-<4**
- KCentra 25 units/kg max. 2500 units

**INR 4-6**
- Kcentra 35 units/kg max. 3500 units

**INR >6**
- Kcentra 50 units/kg max. 5000 units

**INR ≥ 2**
- Vit K 10 mg IV

**Recheck INR within 30 min.**

**INR ≤ 1.4**
- FFP 1-2 U

**INR > 1.4**
- INR > 1.4 at 24 hrs, repeat Vit K 5 mg

**Recheck INR in 15-30 min**

**INR q8h**

**Repeat dosing with Kcentra not recommended**

# For INR 1.7-2, Kcentra can be considered.
Reversal of newer oral anticoagulants

- No specific antidote yet

- Pilot trial of dabigatran reversal agent is being planned

- For now
  - Hemodialysis for dabigatran if within 6 hours
  - 4F- PCC as off label use for apixiban and rivaroxaban.
Emergency ICH management
Principles

- Accelerate removal of blood from the brain
THERAPEUTIC TARGETS IN ICH

- Blood Pressure Control
- Hemostatic Therapies
- Clot Removal
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- Hematoma Expansion
- Mass Effect from Hematoma & Edeema
Audience question

Open craniotomy is currently recommended for which of the following hematomas?

A

B

C

D
Audience question

Open craniotomy is currently recommended for which of the following hematomas?

A

B

C

D
When do I call the neurosurgeon?

- ?? Moderate or large lobar/superficial hemorrhage when deteriorating
- Cerebellar hemorrhage > 3cm with deterioration or brainstem compression and/or hydrocephalus
- Nonsurgical candidates: small ICH / minimal neurologic deficits and a low LOC
How about minimally invasive surgery?
MISTIE- minimally invasive surgery + tpA for ICH evacuation
What happened to Mr. KK?

Pre-surgery  Immediate post op.  1 dose tpa.  48 hours.
180 & 365-Day modified Rankin Scale

180 Day Outcomes:
- Medical:
  - N = 38
  - 0: 21%
  - 1: 11%
  - 2: 14%
  - 3: 14%
  - 4: 14%
  - 5: 14%
  - 6: 14%
- Surgery:
  - N = 52
  - 0: 21%
  - 1: 11%
  - 2: 14%
  - 3: 14%
  - 4: 14%
  - 5: 14%
  - 6: 14%

365 Day Outcomes:
- Medical:
  - N = 25
  - 0: 21%
  - 1: 11%
  - 2: 14%
  - 3: 14%
  - 4: 14%
  - 5: 14%
  - 6: 14%
- Surgery:
  - N = 23
  - 0: 21%
  - 1: 11%
  - 2: 14%
  - 3: 14%
  - 4: 14%
  - 5: 14%
  - 6: 14%
Length of Stay and Cost by Treatment Arm

- **Medical**
  - Length of Stay: 38 days (35%)
  - Cost: $44K (35%)

- **Surgical**
  - Length of Stay: 38 days (35%)
  - Cost: $44K (35%)

Legend:
- Red: ICU
- Blue: Non-ICU
- Green: Surgery
- Non-ICU (Blue)
TPA Accelerates Intraventricular Clot Lysis.
Low-Dose Recombinant Tissue-Type Plasminogen Activator Enhances Clot Resolution in Brain Hemorrhage: The Intraventricular Hemorrhage Thrombolysis Trial
Neal Naff, Michael A. Williams, Penelope M. Keyl, Stanley Tuhrim, M. Ross Bullock, Stephan A. Mayer, William Coplin, Raj Narayan, Stephen Haines, Salvador Cruz-Flores, Mario Zuccarello, David Brock, Issam Awad, Wendy C. Ziai, Anthony Marmarou, Denise Rhoney, Nichol McBee, Karen Lane and Daniel F. Hanley, Jr

Stroke. 2011;42:3009-3016; originally published online August 25, 2011;
How did Mr. KK do?

- Was never intubated
- Went to acute rehab after 3 weeks
- Is now home; in great spirits
- Able to stand with assistance (2 months after ICH), left neglect improving
- Can wheel himself around, cognitively intact, speaking well.
Take home points

1. ICH patients need aggressive treatment in a neuroscience ICU.
2. BP can probably be safely reduced to 140/90 mm Hg over the first 24 hours.
3. Anticoagulation should be promptly reversed.
4. Surgery is indicated only in select patients.
5. Prognostication is best done by an expert keeping in mind that 1/3rd of patients improve up to one year and beyond.
The Stanford Stroke Center