Advances in the Management of Intracerebral Hemorrhage: Evolving Scientific Evidence for Critical-Care Pharmacists

Presented as a Symposium at the 41st ASHP Midyear Clinical Meeting and Exhibition
Program Agenda

Welcome and Introductory Remarks
Jill A. Rebuck, Pharm.D., BCPS, Program Chair and Moderator

Intracerebral Hemorrhage: Etiology, Diagnosis, and Prognosis
Michael N. Diringer, M.D., FCCM

Management of Intracerebral Hemorrhage: Current Conventional Medical and Surgical Interventions
Denise H. Rhoney, Pharm.D., FCCP

Recent Advances in Medical Management of Intracerebral Hemorrhage
Jill A. Rebuck, Pharm.D., BCPS

Questions/ Panel Discussion

Program Faculty

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Program Description

Accounting for more than 10% of all strokes in the United States, intracerebral hemorrhage (ICH) is particularly devastating because it is associated with high morbidity and mortality despite clinical intervention. Understanding the latest science in the management of patients with ICH is important to health-system pharmacists, especially clinical specialists practicing in critical care areas within the hospital.

Many patients with ICH experience an increase in hematoma volume due to subsequent bleeding, and the increase in hematoma volume is an important predictor of mortality and neurological and functional outcomes in these patients. Conventional management of patients with ICH focuses on controlling the intracranial pressure, preventing seizures, limiting cerebral injury, and preventing complications. Recent advances have led to medical therapy that limits hematoma growth, reduces mortality, and improves functional outcomes in patients with ICH.

This symposium will provide an overview of ICH, including morbidity and mortality, risk factors for development of ICH, and prognostic indicators. The objectives of conventional medical and surgical interventions for ICH will be discussed, and recent medical advances will be presented. Speakers will also provide insight into ICH treatment guideline development.

Program Objectives

At the conclusion of this program, participants should be able to:

- List patient risk factors for intracerebral hemorrhage (ICH).
- Discuss prognostic factors in ICH.
- Describe conventional medical management of patients with ICH.
- List limitations of surgical intervention in ICH.
- Using available clinical and pharmacoeconomic studies, describe strategies for incorporating the data into treatment guidelines and protocols for ICH management.

Continuing Education Information

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program provides 2.0 hours (0.20 CEUs) of continuing education credit (program number 204-000-06-431-H01). This program is provided free of charge. After participating in the program, pharmacists may complete the CE test online at the ASHP Advantage CE Testing Center (www.ashp.org/advantage/ce). A passing grade of 70% is required to receive continuing education credit for this program, and pharmacists can print their CE statement immediately. Continuing education credit for this program is available from March 1, 2007, through February 28, 2008.
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Dr. Diringer is President and a founding member of the Neurocritical Care Society, a Fellow of the American Heart Association and of the American College of Critical Care Medicine and a board certified Vascular Neurologist. He is on the Editorial Board of the journals Neurocritical Care and The Neurologist and serves on the board of directors of Mid-American Transplant Services.

Dr. Diringer has lectured throughout the world on acute ischemic and hemorrhagic stroke, subarachnoid and intracerebral hemorrhage, and other severe brain injuries. He is funded by the National Institute of Neurological Disorders and Stroke (NINDS) for research on the clinical pathology of acute brain injury and the use of osmotic therapy after acute central nervous system (CNS) insults.

Dr. Diringer is a prolific writer and has authored or coauthored more than 150 peer-reviewed articles, editorials, book chapters, guidelines and practice parameters for critical care and stroke, abstracts, lectures, and supplements.
Intracerebral Hemorrhage: Etiology, Diagnosis, and Prognosis
Michael N. Diringer, M.D., FCCM

Presentation Abstract

Intracerebral hemorrhage (ICH) accounts for about 8-10% of strokes in Caucasians and as much as 40% of strokes in Asians. The most common cause is poorly controlled hypertension. Other important causes include anticoagulation, cerebral amyloid angiopathy and vascular malformations. Less common causes include sympathomimetic drugs, reperfusion injury, venous occlusion and tumors.

The clinical presentation is similar to ischemic stroke but with several important differences. Headache and seizure at onset are more common in ICH. Consciousness is more frequently impaired, and symptoms may evolve over time. Unlike ischemic stroke, computed tomography (CT) scan is always diagnostic of ICH at presentation. Outcome is also considerably worse than in ischemic stroke. Mortality approaches 40% compared to 5-10% in ischemic stroke. Only about 20% of ICH patients regain independence (versus 60% following ischemic stroke).

A number of factors have been identified which influence prognosis. The most important factors relate to the initial severity of the hemorrhage and include hematoma size, Glasgow Coma Scale score, deep location and intraventricular hemorrhage. Other important prognostic factors include age, hematoma expansion and anticoagulation.

Several factors may contribute to secondary injury after acute ICH. It is now clear that hematoma expansion is very common in the early hours after ICH and leads to clinical deterioration and worse outcome. Although ischemia has been considered an important cause of secondary injury, recent studies suggest that it does not play a role and that cerebral autoregulation is preserved around the hematoma. Recent preliminary work suggests that mitochondrial dysfunction occurs after acute ICH and may account for the cerebrovascular and metabolic changes that occur.
Presentation Objectives

At the conclusion of the program, participants should be able to:

- List the causes of spontaneous intracerebral hemorrhage (ICH).
- Describe the clinical presentation of ICH.
- List at least two prognostic factors in spontaneous ICH.
- Describe at least two potential causes of secondary injury in ICH.
Intracerebral Hemorrhage:
Etiology, Diagnosis, Prognosis
and Secondary Injury

Michael N Diringer, M.D., FCCM
Professor of Neurology, Neurosurgery, Anesthesia & OT
Director, Neurology/Neurosurgery Intensive Care Unit
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Learning Objectives
At the conclusion of the program, participants should be able to:
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• Describe the clinical presentation of ICH.
• List at least two prognostic factors in spontaneous ICH.
• Describe at least two potential causes of secondary injury in ICH.

Proportion of Strokes in U.S.

SAH
3%
ICH
9%
Ischemic
88%

Proportion of Strokes in U.S.
700,000 Strokes per year


Predicted 100% Increase by 2050

No. of Persons

0
25,000
50,000
75,000
100,000

2000
2050

Year


Sites of Spontaneous ICH

Lobes
25%
Basal Ganglia
35%
Thalamus
25%
Pons
7%
Cerebellum
9%


Disclosures
• Research support - NINDS
• Consulting/speaking:
  – Novo Nordisk Inc.
  – Astellas Pharma
• This program is supported by an educational grant from Novo Nordisk Inc.
Higher Mortality and Worse Morbidity than Ischemic Stroke

- 30-day mortality
  - ICH 30-50%
  - Ischemic stroke 5-10%
- Independent
  - ICH 20%
  - Ischemic stroke 60%

Clinical Presentation

- Symptoms may evolve over hours
- Headache common but not always present
- Consciousness often impaired
- Focal signs depend on location
- CT scan diagnostic

Clinical Consequences

- Up to 50% require mechanical ventilation
- Many deteriorate after admission
- Prolonged hospitalization
- Extensive rehabilitation required

Risk Factors for ICH

- Hypertension (especially with poor control)
- Anticoagulation
- Older age
- Cerebral amyloid angiopathy
- Substance abuse
- Smoking
- Renal or liver failure
- Ethnicity

Chronic Hypertension

- Pathology
  - Miliary aneurysms?
  - Lipohyalinosis/fibrinoid necrosis
  - Increased shear in small branches off large vessels
  - Genetic factors

Anticoagulation

- Warfarin indicated in DVT, PE, AF
- Incidence of anticoagulant-associated ICH rose from 5% to 18% of spontaneous ICH in 1990s
- INR 2.5 - 4.5 increases risk of ICH 10X
- Associated with longer interval for ICH expansion
- Doubles ICH mortality

**Hematoma Expansion in Anticoagulated Patients**

<table>
<thead>
<tr>
<th></th>
<th>&lt;1/3 growth (n=20)</th>
<th>≥1/3 growth (n=12)</th>
<th>p value</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>77 (39-89)</td>
<td>70 (46-85)</td>
<td>0.26</td>
<td>76 (39-89)</td>
</tr>
<tr>
<td>Admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>113 ± 21</td>
<td>108 ± 33</td>
<td>0.65</td>
<td>111 ± 26</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>13 (7-29)</td>
<td>12 (5-41)</td>
<td>0.65</td>
<td>12 (5-41)</td>
</tr>
<tr>
<td>GCS score</td>
<td>14 (3-15)</td>
<td>14 (3-15)</td>
<td>0.93</td>
<td>14 (3-15)</td>
</tr>
<tr>
<td>Initial hematoma volume</td>
<td>26</td>
<td>17</td>
<td>0.18</td>
<td>23 (1-135)</td>
</tr>
<tr>
<td>Initial INR correction</td>
<td>2.41</td>
<td>2.36</td>
<td>0.04</td>
<td>2.7 (1.3-9.5)</td>
</tr>
<tr>
<td>Initial rate of INR correction</td>
<td>3.3</td>
<td>4.3</td>
<td>0.19</td>
<td>3.7 (0.3-6.8)</td>
</tr>
</tbody>
</table>

Unpublished Data on File

**Vasculopathies**

- Aneurysm rupture
  - 5-25% have ICH ± SAH
  - MCA aneurysm rupture can mimic hypertensive hemorrhage into deep gray
  - ACA aneurysm rupture – inferior frontal ICH
- AVM
  - 50% present with hemorrhage
  - Any location
- Cerebral Amyloid Angiopathy

**SAH and ICH**

- Occur in about 10% of SAH
- More common with anterior communicating and middle cerebral artery aneurysms

**Vascular Malformations**

Arteriovenous malformations
Cavernous malformations
Dural arteriovenous fistulas

**Cerebral Amyloid Angiopathy**

- Location
  - Lobar hemorrhage
  - Multiple, bilateral
  - Parieto-occipital location
- Associated with dementia/AD
- Elderly patients (>70 years)
- Risk of recurrence 5%-15% annually
- Microbleeds on gradient-echo MRI

**Race: Higher incidence in blacks in the U.S.**

Race: Higher incidence in blacks in the U.S.

More common in Asians


Rate ratios of age-adjusted incidence rates of stroke types by ethnicity in New Zealand, reference group is white New Zealanders/Europeans.

Thrombolytic Therapy

- tPA increases risk of ICH (6% absolute risk in NINDS trial)
- ~20% of bleeds at sites distant from stroke
- Risk factors
  - Age >70 years
  - Serum glucose >300 mg/dL
  - NIHSS >20
  - Early ischemic changes detected on CT


Drug-related

- Cocaine
- Amphetamines
- Phenylpropanolamine
- MAO inhibitors

Causes of ICH: Coagulopathies

- Account for ~10% of ICH
- Anticoagulation for systemic disease
  - ICH is the most important complication
  - Occurs in 1-2% of cases
- Thrombolytics
  - Systemic: rare
  - CNS: 10-20% of cases
- Systemic disease

Causes of ICH: Others

- Reperfusion injury
  - Ischemic stroke
  - Perfusion pressure breakthrough
  - Carotid endarterectomy
- Infection
  - Encephalitis – HSV
  - SBE – mycotic aneurysm
  - Systemic fungal infection
- ICH into tumor

Causes of ICH: Others

- Venous occlusion
  - Dehydration
  - Pregnancy/BCP
  - Protein C deficiency
  - Prothrombin gene mutation
  - Systemic infection
  - Sickle cell trait
Predictors of Outcome

- Glasgow Coma Scale score
- Hematoma volume
- Early hematoma growth
- Intraventricular hemorrhage
- Age
- ICH location (deep)


Predicting Outcome: The ICH Score

<table>
<thead>
<tr>
<th>Component</th>
<th>ICH score</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS (3-4)</td>
<td>2</td>
</tr>
<tr>
<td>GCS (5-12)</td>
<td>1</td>
</tr>
<tr>
<td>GCS (13-15)</td>
<td>0</td>
</tr>
<tr>
<td>ICH volume (cc) &gt;30</td>
<td>1</td>
</tr>
<tr>
<td>ICH volume (cc) &lt;30</td>
<td>0</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>0</td>
</tr>
<tr>
<td>Intratentorial origin</td>
<td>1</td>
</tr>
<tr>
<td>Intratentorial origin</td>
<td>0</td>
</tr>
<tr>
<td>Age (y) &gt;80</td>
<td>1</td>
</tr>
<tr>
<td>Age (y) &lt;80</td>
<td>0</td>
</tr>
<tr>
<td>Total ICH score</td>
<td>0-6</td>
</tr>
</tbody>
</table>

30-day Mortality


Hematoma Volume and Outcome

Good recovery with volume >30 ml does not occur


Cause of Death

- Early mortality
  - DNR orders—prognostic factor bias
  - “Brain death”
- Late mortality
  - Infection - pneumonia
  - Myocardial infarction


Secondary Injury in Patients

Early hematoma growth
- Ischemia
- Mitochondrial dysfunction
- Seizures
- Edema
- Toxic effects of blood products
- Inflammatory response

Hematoma Expansion
Early Hematoma Growth

- Prospective study of ICH growth (n=103)
- Initial CT performed < 3 hours of onset
- Hematoma growth (> 33% ↑ in volume)
  - 26% within 1 hour of baseline CT
  - 12% between 1 and 20 hours
- ICH growth associated with clinical deterioration and worse outcome

Impact of Hematoma Expansion on Outcome

Ischemia

- Primary reduction in CBF
  - Metabolism falls due to inadequate oxygen delivery (ischemia)
  - Characterized by high OEF
- Primary reduction in metabolism
  - Passive secondary fall in CBF
  - Characterized by normal or low OEF

Peri-clot Flow, Metabolism, and OEF

Peri-clot vs. Global

Predictors of ICH Growth
Fujii Y et al. Stroke. 1998;29:1160-1166

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Gender (female/male)</td>
<td>0.48 (0.23-0.98)</td>
<td>0.043</td>
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<tr>
<td>Alcohol consumption (g/d)</td>
<td>1.01 (0.96-1.05)</td>
<td>0.748</td>
</tr>
<tr>
<td>Interval to admission, h</td>
<td>1.00 (0.99-1.01)</td>
<td>0.277</td>
</tr>
<tr>
<td>Consciousness level (vs. baseline)</td>
<td>1.00 (0.99-1.01)</td>
<td>0.277</td>
</tr>
<tr>
<td>Systolic blood pressure at admission, mm Hg</td>
<td>1.00 (0.99-1.01)</td>
<td>0.277</td>
</tr>
<tr>
<td>Shape of hematoma (round/irregular)</td>
<td>0.99 (0.98-1.00)</td>
<td>0.277</td>
</tr>
<tr>
<td>Intraventricular hematoma (yes/no)</td>
<td>1.00 (0.99-1.01)</td>
<td>0.277</td>
</tr>
<tr>
<td>γ-Glutamyl transpeptidase, IUL</td>
<td>1.00 (0.99-1.01)</td>
<td>0.277</td>
</tr>
<tr>
<td>Hemoglobin, mg/dL</td>
<td>0.99 (0.98-1.00)</td>
<td>0.277</td>
</tr>
<tr>
<td>Enhancement of edema sensitivity, μmol</td>
<td>0.99 (0.98-1.00)</td>
<td>0.277</td>
</tr>
</tbody>
</table>

* p < 0.05
+ p = 0.05

Impact of Hematoma Expansion on Outcome

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1.00 (1.00-1.00)</td>
<td>0.001</td>
</tr>
<tr>
<td>Intraventricular</td>
<td>1.00 (1.00-1.00)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Rim of Perihematomal Decreased ADC without Reduced Perfusion**


**Does Reduction of BP Further Reduce CBF in Patients with Acute ICH?**

- Baseline MAP 120 – 150 mm Hg
- Target blood pressure reduction - 15%
- 3 treatment groups of 4 subjects each
  - Control
  - Labetalol
  - Nicardipine

**Effect of Treating Hypertension on CBF following Acute ICH**

![Graph showing % Mean Arterial Pressure vs % Cerebral Blood Flow](image)

**Mitochondrial Dysfunction after ICH**


**Mitochondrial Dysfunction Worsens Over Time**


**Summary**

- ICH has much worse outcome than ischemic stroke
- Initial severity of bleed most important predictor of outcome
- Most common cause poorly controlled hypertension
- Hematoma expansion is an important cause of deterioration
- No ischemia — mitochondrial dysfunction
References


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Denise H. Rhoney, Pharm.D., FCCP received both Bachelor of Science in Pharmacy and
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Following her residencies, she completed a clinical research/drug development fellowship at the
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neuroanesthesia.

Dr. Rhoney is currently Associate Professor of Pharmacy Practice at Eugene Applebaum
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Neuroscience Intensive Care Unit at Detroit Receiving Hospital. She is also the director of the
Cerebrovascular Pharmacology Research Laboratory within the Eugene Applebaum College of
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Management of Intracerebral Hemorrhage: Current Conventional Medical and Surgical Interventions
Denise H. Rhoney, Pharm.D., FCCP

Presentation Abstract

Spontaneous intracerebral hemorrhage (ICH) remains a devastating disease. Despite attempts at improving outcome, overall mortality from ICH remains at an estimated 40% to 50%. Currently there is no accepted medical or surgical therapy for patients with ICH besides early detection of ICH and optimizing supportive care to help prevent complications. Intracerebral hemorrhage is considered a medical emergency and initial goals should be directed towards stabilization and principles of airway, breathing and circulation. Cornerstones in the medical management of these patients include: blood pressure reduction, intracranial pressure reduction, fever control, blood glucose control, adequate nutritional support, osmotherapy, reversal of anticoagulation, and prevention of thrombotic or gastrointestinal complications. Reduction of mass effect through hematoma clot evacuation was traditionally thought to be a common treatment approach. However, the International Surgical Trial in Intracerebral Hemorrhage (STICH) showed no benefit in outcomes of patients who underwent surgical evacuation compared with patients who received conservative supportive care. Pharmacists may play a key role in preventing and managing ICH. One of the most important roles is in counseling and promoting adherence to pharmacotherapeutic regimens. During the acute period, prevention of both intracranial and extracranial complications is essential, and the pharmacist should diligently monitor these patients for appropriate regimens and timely interventions. A multidisciplinary approach for development of quality indicators for these complications and/or standardized order sets may improve the quality of care of these patients.
Presentation Objectives

At the conclusion of the program, participants should be able to:

- Discuss the role of acute blood pressure reduction following intracerebral hemorrhage (ICH).
- Design a treatment approach for managing increases in intracranial pressure following ICH.
- Identify the role of prophylactic regimens, including prophylaxis of seizure, venous thromboembolism, and gastrointestinal bleeding, in the management of patients with ICH.
- Develop a treatment approach for managing ICH associated with anticoagulants.
- Describe the role of surgical therapy in the management of patients with ICH.
Management of Intracerebral Hemorrhage: Current Conventional Medical and Surgical Interventions

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Disclosure

- Research support
  - NINDS
  - FDA Orphan Drug Program
  - Society of Critical Care Medicine
  - PDL Biopharma, Inc.
  - UCB, Inc.
- Consulting/speaking
  - PDL Biopharma, Inc.
  - Novo Nordisk Inc.
- This program is supported by an educational grant from Novo Nordisk Inc.

Learning Objectives

At the conclusion of the program, participants should be able to:
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- Design a treatment approach for managing increases in intracranial pressure following ICH.
- Identify the role of prophylactic regimens, including seizure, venous thromboembolism, & gastrointestinal bleeding, in the management of patients with ICH.
- Develop a treatment approach for managing ICH associated with anticoagulants.
- Describe the role of surgical therapy in the management of patients with ICH.

Intracerebral Hemorrhage

ichaemorrhage trauma Ischemic stroke Ischemic stroke

- ICH mortality ~30-50% at 1 month; 50% at 1 yr
- Ischemic stroke mortality ~ 5-10% at 1 month
- Only 20% of ICH patients independent at 6 months
- Cost of ICH is US$125,000/year/patient → $6 billion annually

Chest 2001;119:302s; Stroke 1999;30:905-915

Management Goals

- Prevent hematoma expansion
- Reduce mass effect
- Minimize secondary neurological injury
- Prevent and treat of medical complications
- Initiate early rehabilitation

Course of Neurologic Consequences from ICH
Intracerebral Hemorrhage

Initial Stabilization

- Focus on ABC’s
  - Rapid neurologic decline & depressed consciousness necessitate endotracheal intubation and mechanical ventilation
  - Rapid sequence intubation (avoid agents that ↑ ICP)
  - Avoid aggressive early hyperventilation (P<sub>CO2</sub> < 28 mm Hg)
- Fluid: goal = euvoelema and optimization of CPP
  - Avoid glucose containing and hypotonic fluids
  - 0.9% NaCl
  - 3% NaCl/Na acetate - ? Patients with perihematomal edema and mass effect
- Neurological monitoring
- Admission to neurologic intensive care unit

Surgical Management

- Goal of surgery
  - Clot removal & limit secondary insult of hematoma
- Craniotomy
  - Standard approach
  - Adequate exposure to clot
  - Invasive
- Minimally invasive surgery
  - Newer approach
  - Used ± thrombolitics
- Ventricular catheter
  - Standard in patients with IVH or hydrocephalus
  - Used ± thrombolitics

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage

A Statement for Healthcare Professionals From a Special Writing Group of the Stroke Council, American Heart Association

Joseph P. Blocker MD, Robert A. Adams, MD, William Barrow, MD, William Feindel, MD, Edward Fischl, MD, James Frost, MD, Charles Hane, MD, Daniel Kaczer, MD, Marc Macklin, MD, Barbara Taylor, MD, Joseph S. Zghiche, MD, Jatinder Zimberoff, MD

Few Recommendations based upon “Level 1” evidence

- Authors state that guidelines should be used for a basis for future clinical trials

Recommendations for the Management of Intracranial Haemorrhage – Part I: Spontaneous Intracerebral Haemorrhage

The European Stroke Initiative Writing Committee and the Writing Committee for the EUS Executive Committee
Surgical Management
Review of Clinical Trials

Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial

- Landmark study 1033 ICH patients
- Randomized to early surgical treatment vs. conservative medical management
- Most patients had open craniotomy
- No benefit of early surgery


STICH TRIAL

Operate

Young patient
Non-dominant clot
Initially talking
Deterioration GCS from 9-12 to ≤ 8
Superficial lobar clot
Cerebellar hemorrhage > 3 cm

Do not operate

Elderly patient
Dominant clot
Coma from outset
Extending to pain
Deep thalamic clot

Emergency Management
Reversal of Anticoagulation

- Warfarin use associated with 15% of all ICH
- Warfarin-treated patients have increased risk of hematoma expansion and is associated with worse outcome
- Intensity of anticoagulation independently predicts 3-month mortality
- Treatment based upon D/C warfarin and various reversal strategies
  - Vitamin K
  - Fresh frozen plasma (FFP)
  - Prothrombin complex concentrate (PCC)
  - Recombinant Factor VIIa (rFVIIa)
  - No prospective comparative randomized trials
- Goal = prompt normalization of INR

**Warfarin Reversal**

**Vitamin K**
- Effective response usually 2-6 hrs (up to 24 hr)
- Should use in combination with other coagulation factors
- IV administration (5-20 mg)
  - Anaphylaxis rare (3 per 10,000 doses)

**Steiner T, et al. Stroke 2006;37:256-62.**

**Warfarin Reversal**

**Fresh Frozen Plasma**
- Contains all clotting factors (non-concentrated)
  - Content vitamin-K dependent clotting factors in each unit vary
- Standard requirement of 15 mL/kg
- Requires thawing, compatibility testing
- Complications
  - Volume overload (may require 800-3,500 mL)
  - Infection
  - Transfusion-related adverse events
- Retrospective analysis reported a median time for door to INR normalization of 30 hours with 8% of patients experiencing hematoma progression despite INR normalization

**Warfarin Reversal**

**PCC**
- Contains coagulation factors VII, IX, X, prothrombin, and protein C, S, Z
- Reconstituted product 50-150 mL
- Small studies suggest PCC more effective than FFP
  - Incidence and extent of hematoma growth lower in patients treated with PCC possibly related to faster INR normalization
  - No overall improvement in outcome
- PCC availability limited in US
- Reported cases of DIC and thrombosis

**Steiner T, et al. Stroke 2006;37:256-62.**

**Warfarin Reversal Chest Guidelines**

**Anticoagulation Reversal**

**EUSI ICH Guidelines**

**Emergency Management**

**Coagulopathic Patient**

**Normalisation of INR**
- PCC: 40 mL/kg min dose 60 mL/kg
- FFP: 20 mL/kg to achieve 0.2-0.4 INR, or a INR of 1.5-2.1, or a INR of 0-6.6 to 1.0
- Vitamin K: 1-2 mg IV or subcutaneous

**Normalisation of FFP after heparin**
-_hemorrhage_ APTT: 1.5 x reference; INR: 1.5 x reference

**Cerebrovasc Dis 2006;22:294-316.**

Oral Anticoagulant Related ICH

Unresolved Issues

- Effective treatment regimen
- Appropriate time window for treatment
- Monitoring of treatment effect
  - Is INR the best method?2
  - INR does not reflect all vitamin K-dependent clotting factors
- Adverse effects associated with intervention
- Re-initiation of anticoagulant therapy
  - Decision analysis suggested risk of recurrent ICH outweighs benefit in patients with nonvalvular a.fib. and history of lobar hemorrhage1
  - If restarted, many suggest after 10-14 days2


Emergency Management

Acute Blood Pressure Control

- BP elevation very common early in ICH
  - 1/3 of patients hypertensive on 10th day
- Admission elevated SBP is associated with ↑ risk of poor outcome
- Urgent need for studies evaluating optimal BP target and agents for treating acute hypertension in patients with ICH
  - ATACH trial ongoing http://www.strokecenter.org/trials/7th/Results.aspx?i=43
  - Enrolled patients will be administered anti-hypertensive treatment to reduce SBP to 170-200 mm Hg. Following success of this, patients will be graduated to the next two levels of blood pressure reduction (140-170 mm Hg and 110-140 mm Hg)
- Considerations in lowering BP
  - Potential benefits:
    - May ameliorate local edema
    - May limit early hematoma growth
  - Potential risk:
    - Aggravation of perilesional ischemia


Emergency Management

Acute Blood Pressure Control

- Treatment guidelines
  - AHA guidelines1
    - If SBP > 160-230 mm Hg, DBP < 105-140 or MAP ≥ 130 mm Hg then institute IV titratable agents
    - Maintain CPP > 70 mm Hg (if ICP monitoring is available)
  - EUSI guidelines2 (class IV evidence)
    - Patients with known HTN or signs of chronic HTN
      - Treat SBP > 180 mm Hg and/or DBP > 105 mm Hg
      - Target BP 170/100 mm Hg (MAP 125 mm Hg)
    - Patients without known HTN
      - Treat SBP > 160 mm Hg and/or DBP > 95 mm Hg
      - Target BP 150/90 mm Hg (MAP 110 mm Hg)
    - Reduction of MAP > 20% should be avoided
    - Guarantee sufficient CPP > 70 mm Hg


Cerebral Autoregulation

- Patients with chronic hypertension autoregulate cerebral blood flow around higher set points
- Patients with cerebral ischemia lose their ability to autoregulate


Acute Blood Pressure Control

- BP and early hematoma growth
  - 9% hematoma growth reported in 27 ICH patients with SBP <160 mm Hg and DBP <90 mm Hg1
  - SBP 160-180 mm Hg have shown a relationship to hematoma growth2-3
- Perihematoma ischemia after ICH
  - PET and MRI studies have not shown evidence of perihematomal tissue ischemia4-7
  - PET studies confirmed autoregulation intact in perihematomal regions after acute ICH8


BP Management in ICH

Therapeutic Options

- Mechanism of vasodilatory increases in ICP


Emergency Management

Acute Blood Pressure Control

- Mechanism of vasodilatory increases in ICP


BP Management in ICH
Therapeutic Options

- Retrospective analysis of 90 stroke patients (51.6% ICH)
- Patients who achieved goal BP in first 60 minutes

- Dosage adjustments (p < 0.001)
  - Labetalol = 4 (1-17)
  - Nicardipine = 2 (0-5)
- Need for additional BP agents (p=0.013)
  - Labetalol = 33% Nicardipine = 8%


Mechanisms for Elevated ICP

- Increase in brain water due to edema
- Expanding masses such as a tumor, hematoma or abscess
- Increase in cerebral blood volume due to arterial vasodilatation or venous outflow obstruction
- Increased CSF due to increased production, impaired absorption, or flow obstruction.

Treatment Thresholds

- Intracranial pressure
  - Insufficient data to support a treatment standard
  - Guideline
    - ICP treatment should be initiated at an upper threshold of 20-25 mm Hg
    - Option
      - Interpretation and treatment of ICP based on any threshold should be corroborated by frequent clinical examination and CPP data
- Cerebral perfusion pressure (CPP= MAP-ICP)
  - Insufficient data to support a treatment standard
  - Guideline
    - CPP should be maintained at a minimum of 60 mm Hg. In the absence of cerebral ischemia, aggressive attempts to maintain CPP above 70 mm Hg with fluids and pressors should be avoided because of the risk of adult respiratory distress syndrome.


Intracerebral Hemorrhage
Cerebral Edema

- Edema develops early and peaks days to weeks later

- Several mechanisms implicated
  - Early phase (plasma protein accumulation)
  - Second phase (complement activation/thrombin, inflammation)
  - Late phase (hemoglobin toxicity)


Mechanisms of Cerebral Edema

- Impending cerebral herniation
  - Use of hyperventilation and osmotic agents shown to improve outcome
  - Corticosteroids shown no benefit on outcome, but complications (infections and hyperglycemia) are more common
  - Glycerol 10% 500 ml has no effect on outcome


Cerebral Edema
Emergency Management

- Impending cerebral herniation
  - Use of hyperventilation and osmotic agents shown to improve outcome
  - Corticosteroids shown no benefit on outcome, but complications (infections and hyperglycemia) are more common
  - Glycerol 10% 500 ml has no effect on outcome
Cerebral Edema Osmotic Therapy

- Mannitol is “standard” therapy
- Mechanisms of action
  - Early effects related to changes in blood viscosity or rheologic effects
    - Plasma expansion and increased oxygen delivery cause a compensatory vasoconstriction and reduction in cerebral blood volume, which lowers ICP
  - Later effect is the establishment of an osmotic gradient with the subsequent removal of water from the brain interstitium into the intravascular space


Osmotherapy Comparison

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mannitol</th>
<th>Hypertonic Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus Dosing</td>
<td>0.25 – 1 gm/kg over 20 min</td>
<td>23.4%</td>
</tr>
<tr>
<td>Continuous Infusion</td>
<td>Not recommended</td>
<td>2-3% at 0.1-1mL/kg/hr</td>
</tr>
<tr>
<td>Onset of Effect</td>
<td>15-30 min</td>
<td>15-30 min</td>
</tr>
<tr>
<td>Duration of Effect</td>
<td>Not established</td>
<td>Not established</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Diuresis, renal failure, rebound ICP, hypotension, reverse osmosis</td>
<td>Electrolyte abnormalities, rebound ↑ ICP, CRP, bleeding complications</td>
</tr>
<tr>
<td>Risk of Hypovolemia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Advantages</td>
<td>Clinical experience</td>
<td>↑ CO &amp; ↓ PVR; ↓ afterload, antiinflammatory properties, augments intravascular vol</td>
</tr>
</tbody>
</table>


ICP Management General Care Issues

- Elevate head of bed 30°
- Use only isotonic fluids (0.9% saline)
- Control fevers aggressively
- Seizure prophylaxis
- Normoglycemia

Option: 2.3% saline (1-2 mL/kg/hr) or mannitol (1-1.4 g/kg/dh) for target Na+ 145-155 mEq/L and osmolality 300-320 mOsm/L

ICP Management Stepwise Protocol

1. Surgical decompression
   - consider repeat CT scanning and definitive surgical intervention or ventricular drainage
2. Sedation
   - intravenous sedation to attain a motionless, quiet state
3. CPP optimization
   - pressor infusion if CPP is < 70 mm Hg, or reduction of blood pressure if CPP is > 110 mm Hg


ICP Management Stepwise Protocol

4. Osmotherapy
   - mannitol (0.25 – 1.5 g/kg IV or 0.5-2.0 mL/kg) and 23.4% hypertonic saline (repeat every 1-6 h as needed)
5. Hyperventilation
   - target pCO2 26-30 mm Hg
6. High dose pentobarbital therapy
   - load with 5-20 mg/kg, infuse 1-4 mg/kg/h
7. Hypothermia
   - cool core body temperature to 32-33°C


Medical Management Seizures

- Seizures reported to occur in 2.8-18% of patients
- Most seizures occur early (24-72 hrs)
- Many patients may have “Nonconvulsive” seizures
  - Continuous EEG monitor 63 patients with ICH
  - Nonconvulsive seizures ~ 28% (4X clinical rate)
  - Patients with nonconvulsive seizures had poorer outcomes
  - All patients had phenytoin prophylaxis
- AHA ICH guidelines suggest phenytoin prophylaxis for 1 month
  - No randomized trials have addressed efficacy
  - Observational study suggested low frequency of seizures in patients with lobar ICH given prophylactic AED
- European ICH guidelines
  - Early prophylactic treatment not recommended but may be considered for selected patients with lobar ICH

Medical Management

Fever Control

• Sustained fever after ICH independently associated with poor outcome
• Guidelines
  – AHA ICH guidelines: Treatment of temp > 38.5°C
  – EUSI ICH guidelines: Treatment of temp ≥ 37.5°C
• No human data evaluating hypothermia in ICH
  – Delayed rather than early hypothermia is beneficial after ICH in animal models

Medical Management

Nutritional Requirements

• Early enteral nutrition in dysphagic stroke patients resulted in 6% mortality reduction compared to avoidance of enteral feeding in first week
• Energy expenditures were reported to approximate TBI patients in first week
• TBI guidelines
  – Replace 140% of resting metabolism expenditure in nonparalyzed patients and 100% of resting metabolism expenditure in paralyzed patients
  – Enteral or parenteral formulas should be used that contain at least 15% of calories as protein by the 7th day of injury

Medical Management

Glucose Control

• Normalization of serum glucose is recommended
  – Hyperglycemia is risk factor for poor outcome
  – Hyperglycemia produces brain edema and perihematomal cell death in experimental ICH
• Optimal level of glucose is unknown
• Metabolic consequences of intensive glycemic control in ICH unknown
  – Sub-group analysis of van den Berghe’s study suggested better long-term outcomes in patients with a variety of CNS disease
  – Intensive control (80-100 mg/dL) was compared to loose control (120-150 mg/dL) in TBI patients

Medical Management

Glucose Control

• Results of TBI study
  – 70% reduction in microdialysis glucose in intensive control group
  – No change in global metabolic rate of glucose
  – Increase in OEF in intensive control group (Table 2)
  – Increase in microdialysis markers of brain metabolic distress (Table 4)
  – No differences in mortality or functional outcome

Table 2. Comparison of microdialysis glucose and markers of brain metabolic distress in intensive and control group

<table>
<thead>
<tr>
<th>Timepoints</th>
<th>Group</th>
<th>Glucose</th>
<th>OEF</th>
<th>Distress Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Int.</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>24h</td>
<td>Int.</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>48h</td>
<td>Int.</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>72h</td>
<td>Int.</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

Prophylaxis of Medical Complications

Venous Thromboembolism

• High risk for DVT and PE

• Benefit of prophylaxis must be balanced with potential risk of increased hemorrhagic complications
  – Analysis of bleeding risk factors in NCCU patients receiving VTE prophylaxis
    – BE occurred in 14.9% patients a median 3 days after initiation of LDUFH and incidence of DVT/PE was 2% (N=181)
    – LDUFH was initiated within 24 hrs of hospital admission in 84% of patients
    – Independent risk factors for bleeding: MV and NSAID use

Reference

Prophylaxis of Medical Complications
Venous Thromboembolism

Prophylaxis regimen trials in ICH patients
- Small prospective study heparin (5,000 U q12h) started on day 2 reduced incidence of DVT/PE with no increase in intracranial bleeding compared to starting on day 101
- IPC significantly decreased occurrence of asymptomatic DVT all day 10 compared to elastic stockings in ICH patients2
- AHA ICH guidelines3
- Pneumatic devices decrease the risk of PE during hospitalization
- EUSI ICH guidelines4
- Compression stocking & IPC are recommended for prevention
- Low-dose heparin or LMWH should be considered after 24 hrs (Class IV evidence)


Stress-Related Mucosal Damage

Risk factors for GI bleeding in critically ill patients 1-3
- Mechanical ventilation (esp. >3 days) Coagulopathy
- Major trauma/polytrauma Shock (any type)
- Sepsis/septic shock Severe burns (>30%)
- Head trauma or spinal trauma Neurosurgery
- Multiple organ failure (hepatic, renal, etc.)
- Predictors of GI bleeding in ICH patients4
- Size of hematoma
- Septicemia
- GCS score
- No randomized trials of SRMD prophylaxis in ICH patients


Therapeutic Approaches to SRMD Prophylaxis

Significant Risk for Stress-Related Mucosal Disease

Supportive Care
- Correction of any shock-like state
- Correction of acid-base imbalance
- Maintenance of global oxygenation
- Adequate nutritional support

Antacids
Sucralfate
Proton Pump Inhibitors
H2RAs

Prophylaxis

Role of Secondary Prevention

Hypertension
- Level A - diagnosis and control of HTN strongly recommended
- Level A - BP should be lowered after ICH with diuretic and ACE-I

Lifestyle changes
- Class IV - despite lack of evidence recommended weight reduction program, smoking cessation, and low sodium diet
- Alcohol intake
  - Class IV - discourage excessive use of alcohol
- Antiplatelet agent use
  - Class IV - balance risk vs. benefits

Secondary Prevention Hypertension

- Systolic Hypertension in Elderly Program Study (SHEP)
  - Treatment of hypertension reduced risk of ICH by 90%
- Perindopril Protection Against Recurrent Stroke Study (PROGRESS)
  - 6,105 stroke patients randomized to either placebo or perindopril ± indapamide

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=3054)</th>
<th>Perindopril (n=3016)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Fixed effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>138 (124-153)</td>
<td>136 (123-151)</td>
<td>0.022</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>137 (123-152)</td>
<td>135 (122-150)</td>
<td>0.009</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>136 (122-151)</td>
<td>134 (121-149)</td>
<td>0.006</td>
</tr>
</tbody>
</table>


Future Directions

Other Medical Research Priorities:
- Treatment of hyperglycemia
- Normalization of body temperature
- Administration of AEDs
- Safety of DVT prophylaxis

Intracerebral Hemorrhage

Summary

- Appropriate management of ICH is unknown due to a paucity of clinical trials.
- There is an urgent need for prospective, randomized trials to assess the most appropriate management strategies along with addressing underlying mechanisms of brain injury.
- Until more data are available, the onus remains on the clinician to make the best possible judgement when managing ICH patients.
References


Advances in the Management of Intracerebral Hemorrhage: Evolving Scientific Evidence for Critical-Care Pharmacists

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Critical Care Clinician
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Associate Professor of Surgery
University of Vermont College of Medicine
Burlington, Vermont

Jill A. Rebuck, Pharm.D., BCPS, is a Surgical Critical Care Pharmacist Clinician in the Department of Pharmacotherapy at Fletcher Allen Health Care and an Associate Professor of Surgery and the Director of Surgical Research in the Division of Trauma/Critical Care at the College of Medicine of the University of Vermont, in Burlington, Vermont. She practices daily in a multidisciplinary surgical intensive care unit with a specific practice interest in trauma and neurological emergencies.

After receiving her Bachelor of Science in Pharmacy and Doctor of Pharmacy degrees from the Philadelphia College of Pharmacy and Science in Philadelphia, Pennsylvania, Dr. Rebuck completed a Pharmacy Practice Residency at Detroit Receiving Hospital and University Health Center in Detroit, Michigan. This was followed by a Critical Care Specialty Residency at the University of Colorado Health Science Center in Denver, Colorado, and a 2-year Critical Care Pharmacotherapy Fellowship at the University of Nebraska College of Pharmacy in Omaha, Nebraska.

Dr. Rebuck is actively engaged in leadership, including serving as the current Chair of the Society of Critical Care Medicine Clinical Pharmacy and Pharmacology Section and President-Elect of the Vermont Society of Health-System Pharmacists. She is board certified in Pharmacotherapy and has been awarded fellowship in the American College of Critical Care Medicine.

Dr. Rebuck has spoken at numerous regional and national scientific and professional meetings on critical care topics of interest, including those related to trauma, hemostasis, and neurological injury. Dr. Rebuck has published over 80 original research abstracts and scientific articles in leading medical and pharmacy journals. She has received various research, practice, and teaching awards, including Pharmacist of the Year.
Recent Advances in Medical Management of Intracerebral Hemorrhage
Jill A. Rebuck, Pharm.D., BCPS

Presentation Abstract

In recent years, there has been an enhanced interest in evaluating new and emerging therapeutic options for the treatment of hemorrhagic stroke and intracerebral hemorrhage (ICH). One experimental option involves a role for thrombolytic therapy in ICH to reduce the hematoma volume, supplement endogenous fibrinolysis, reduce deleterious breakdown products, and improve neurological outcome. Small studies have demonstrated promising results of local delivery of thrombolytics, specifically rt-PA and urokinase, directly into the hematoma during minimally invasive surgery. Another emerging option for ICH encompasses early hemostatic therapy with antifibrinolytics or recombinant activated factor VIIa (rFVIIa). Unfortunately, limited data available for aminocaproic acid in reducing hematoma expansion demonstrated suboptimal efficacy. Recent clinical trial data support rFVIIa as a new therapy for the treatment of spontaneous ICH as evidenced by limiting hematoma growth, reductions in mortality, and enhancement of functional outcomes. A practical challenge related to rFVIIa therapy is the need to administer the drug within four hours of ICH symptom onset. Another important consideration of rFVIIa therapy is the potential for increased arterial thromboembolic events, such as cerebral infarction and myocardial ischemia. An ongoing study, the FAST trial, is exploring rFVIIa efficacy and safety more definitively. This therapeutic approach represents an expensive modality, yet no other medical therapy has demonstrated a significant effect on patient outcome in ICH. A preliminary pharmacoeconomic evaluation of rFVIIa suggests cost-effectiveness based on a decision analytical model. Development of institutional guidelines for rFVIIa with active pharmacy involvement will lead to safe, cost-effective therapy for the patient population most likely to improve from such therapy while minimizing therapy in patients less likely to benefit to ensure maximization of a benefit-to-risk analysis. The pharmacist is an essential practitioner in the treatment of patients suffering from an ICH and practical clinical application of available data will be discussed.
Presentation Objectives

At the conclusion of the program, participants should be able to:

- List agents in clinical trials for the management of patients with intracerebral hemorrhage (ICH).
- Discuss the patient population most likely to benefit from recombinant activated factor VIIa (rFVIIa) therapy in the setting of ICH.
- Describe the limitations of rFVIIa therapy during ICH, focusing on timing of administration and thromboembolic safety concerns.
- Evaluate the available literature associated with early hemostatic therapy and apply knowledge gained to the development of ICH treatment guidelines.
Recent Advances in Medical Management of Intracerebral Hemorrhage (ICH)

Jill A. Rebuck, Pharm.D., BCPS
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Associate Professor of Surgery
University of Vermont College of Medicine
Chair, Society of Critical Care Medicine CPP Section

Disclosure
• Advisory Board, Novo Nordisk Inc.
• This program is supported by an educational grant from Novo Nordisk Inc.

Learning Objectives
At the conclusion of the program, participants should be able to:
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• Describe the limitations of rFVIIa therapy during ICH, focusing on timing of administration and thromboembolic safety concerns.
• Evaluate the available literature associated with early hemostatic therapy and apply knowledge gained to the development of ICH treatment guidelines.

Early Hemostatic Therapy
• Early hematoma growth common in ICH
• Early hemostatic therapy
  – Prevent early clot expansion
  – Reduce late neurologic deterioration from edema
• Ideal agent
  – Inhibits fibrinolysis
  – Local activation of coagulation
  – Fast onset
  – Few adverse events
• Aminocaproic Acid
• Recombinant Factor VIIa (rFVIIa)

Aminocaproic Acid (ACA) in ICH
• Primary outcome hematoma expansion (HE)
  – Defined as > 33% of baseline volume
• Open label pilot study - 9 control patients vs. 5 patients treated with ACA
• Study group treated with 5 grams IV ACA bolus then 1 gram/hr x 23 hours
  – No thrombotic or other serious adverse events
• HE in 22% of control vs. 60% ACA patients
• Study halted after futility analysis

**Early Hemostatic Therapy rFVIIa**

1. rFVIIa works at site of vascular injury, where TF is expressed & activated platelets are found
2. In pharmacological doses, rFVIIa binds directly to surface of activated platelets & activates FX to FXa, resulting in a burst of thrombin generation
3. rFVIIa enhances localized thrombin generation & fibrin clot formation, producing a stable fibrin clot


**rFVIIa in ICH: Phase IIA US Study**

- R, DB, MC, PC trial
- N=40 ICH + head CT < 3 hrs after Sx onset
- rFVIIa dose-escalation (5, 20, 40, or 80 mcg/kg) or placebo (n=8 in each)
- 10 thromboembolic events
  - Similar across groups, no dose relationship
- No consumption coagulopathy
- No increase in edema-to-ICH volume ratio


**Safety and Feasibility of Recombinant Factor VIIa for Acute Intracerebral Hemorrhage**

- Phase II R, DB, MC, PC dose escalation study (N=48)
- 6 dosing tiers (n=6 in each) 10, 20, 40, 80, 120, 160 mcg/kg rFVIIa vs. placebo (n=12)
- One-time dose within 4 hours of onset of symptoms
- Primary outcome: frequency of adverse events
  - Thrombotic events
  - Brain edema
- Safety assessment: serial ECG, troponin I, coagulation testing, LE Doppler U/S, & edema:ICH volume ratio
- Conclusions: rFVIIa well tolerated


**Efficacy of rFVIIa in Acute ICH**

- Baseline CT scan
- 24 hours
- 90 days
- rFVIIa 80 mg/kg x 3 doses or placebo
- Patients presenting with acute large ICH
- 20 Countries
- 73 Trial Sites


**Dose-Ranging rFVIIa Study: Preventing Early Hematoma Growth in Acute ICH**

- M, et al. NEJM 2005

**ICH Study: Exclusion Criteria**

- GCS 3 - 5 (deep coma)
- Hematoma evacuation planned < 24 hrs
- Hx: thrombocytopenia, coagulopathy, sepsis, crush injury, DIC, oral anticoagulant use
- Symptoms of thrombotic or vaso-occlusive disease
  - Angina, claudication, DVT, CVA, MI
- Secondary ICH related to
  - Aneurysm
  - Arteriovenous malformation
  - Trauma

Baseline Characteristics

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Placebo</th>
<th>40 mcg/kg</th>
<th>80 mcg/kg</th>
<th>160 mcg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>96</td>
<td>108</td>
<td>92</td>
<td>103</td>
</tr>
<tr>
<td>Male</td>
<td>53%</td>
<td>63%</td>
<td>61%</td>
<td>67%</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>68 ± 12</td>
<td>67 ± 12</td>
<td>65 ± 12</td>
<td>64 ± 13</td>
</tr>
<tr>
<td>White</td>
<td>81%</td>
<td>77%</td>
<td>86%</td>
<td>80%</td>
</tr>
<tr>
<td>Asian</td>
<td>15%</td>
<td>19%</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>ICH volume (mL)</td>
<td>24 ± 22</td>
<td>22 ± 22</td>
<td>23 ± 24</td>
<td>26 ± 30</td>
</tr>
<tr>
<td>Treated &lt; 3 hr after symptom onset</td>
<td>72%</td>
<td>62%</td>
<td>76%</td>
<td>71%</td>
</tr>
</tbody>
</table>


Results: Timing of rFVIIa Administration

Treatment intervals
- Mean onset-to-CT interval: 114 ± 35 min
- Mean CT-to-trial drug interval: 54 ± 21 min
- Mean onset-to-trial drug interval: 167 ± 32 min


Estimated 24 hr Mean % ICH Change

Percent change in ICH volume: Baseline → 24 hours

- Placebo: 29%
- 40 mcg/kg: 16%
- 80 mcg/kg: 14%
- 160 mcg/kg: 11%
- Combined rFVIIa Groups: 14%


90 day Mortality: Acute ICH

<table>
<thead>
<tr>
<th>Placebo</th>
<th>40 mcg/kg</th>
<th>80 mcg/kg</th>
<th>160 mcg/kg</th>
<th>Combined rFVIIa Groups</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>29%</td>
<td>18%</td>
<td>18%</td>
<td>19%</td>
<td>18%</td>
<td>0.02</td>
</tr>
<tr>
<td>RR 38%</td>
<td>38%</td>
<td>34%</td>
<td>38%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Combined rFVIIa vs placebo


Modified Rankin Scale (Day 90): “Left Shift”

- Score 4–6: 69%
- Placebo: 69%
- 40 mcg/kg: 55% (P = 0.02)
- 80 mcg/kg: 49% (P = 0.008)
- 160 mcg/kg: 54% (P = 0.02)

NNT* 7.1

NNT to avoid 1 death or severe disability outcome

Barthel Index at Day 90

<table>
<thead>
<tr>
<th>Placebo</th>
<th>40 mcg/kg</th>
<th>80 mcg/kg</th>
<th>160 mcg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>25</td>
<td>55</td>
<td>68</td>
</tr>
<tr>
<td>P</td>
<td>0.07</td>
<td>0.03</td>
<td>P = 0.02</td>
</tr>
</tbody>
</table>

- 0 (completely dependent) to 100 (independent in Activities of Daily Living)
- Barthel index of 60 – 90, assisted independence
- Dead patients were assigned a Barthel Index score of 0

Serious Thromboembolic Events: ICH rFVIIa Study

<table>
<thead>
<tr>
<th>Placebo</th>
<th>40 mcg/kg</th>
<th>80 mcg/kg</th>
<th>160 mcg/kg</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 %</td>
<td>6 %</td>
<td>4 %</td>
<td>10 %</td>
<td>7 %</td>
</tr>
</tbody>
</table>

P= 0.12 vs. placebo

- Independent safety board; all events within 90 days captured
- 23 patients experienced 26 serious thromboembolic events

Arterial & Fatal Thromboembolic Events: ICH rFVIIa Trial

- 2% fatal or disabling adverse events in both groups
- Arterial thromboembolic events occurred significantly (P = 0.01) more frequently with rFVIIa (5%) vs. placebo (0%)
  - Cerebral infarction (9) & myocardial ischemic events (7)
  - All but 4 within 72 hrs of rFVIIa
  - 2 strokes were fatal, 5 had significant disability
  - Only 1 of the cardiac events was significant

rFVIIa- Mayer et al. Considerations

- 1st medical trial to show significant effect on outcome in ICH
  - rFVIIa limits hematoma growth
  - Reduction in mortality, improve functional outcome
- Effect is time-related
- Arterial thrombosis concerning
- Await results of FAST (Phase III trial)
  - 20 vs. 80 mcg/kg vs. placebo

General Safety Considerations rFVIIa

- Increased risk: DIC, advanced atherosclerotic disease, crush injury, or septicemia
  - Due to circulating TF or predisposing coagulopathy
- Adverse event reporting
  - 185 events/approx. 10,000 patients in 5 years
    - Arterial 54.1%
      - CVA (39), AMI (34), other arterial (26)
    - Venous 40.4%
      - PE (32), DVT/other (42)
    - Device occlusion 5.5%

rFVIIa: Drug Expense

- Acquisition cost: $0.94/mcg (JR institution)
  - Cost for 70 kg patient (rounding down to nearest vial)
    - 20 mcg/kg = $1,316
    - 40 mcg/kg = $2,632
    - 80 mcg/kg = $5,264
- Practical considerations for reducing cost
  - Multidisciplinary guidelines
  - Rounding to nearest vial size (1.2, 2.4, 4.8 mg)
  - Only prepare 1 dose at a time (3 hr stability once reconstituted)

rFVIIa Cost-Effectiveness in ICH

- Decision-analytic model, HCUP & Medicare data
  - After IC/EC met + CT diagnosis of ICH, patients in model: placebo or rFVIIa 40, 80, or 160 mcg/kg; 70 kg weight
- Short-term: per-day hospital costs estimated from 5% sample of Medicare database → LOS → Cost of hospitalization per each mRS category
- Long-term (>90d): long-term stroke-specific cost multipliers
- Utilities weights specific to mRS scores + sensitivity analysis
- Treatment of ICH + rFVIIa 40 mcg/kg = cost-effective
  - Cost-effectiveness ratio of $6,308/QALY
- Treatment of ICH + rFVIIa 80 mcg/kg = cost-saving of $5,866
  - Gain of 1.67 QALYs


rFVIIa Therapy for Anticoagulant Reversal

- No RCT data currently available
- 15 - 20 mcg/kg IV sufficient for warfarin reversal
  - Recommend 1.2 mg vial IV bolus
  - Rapid INR reversal & bleeding cessation
- 90 mcg/kg IV in normal volunteers s/p fondaparinux or idraparinux
  - Result in thrombin generation & PT/PTT correction

Warfarin Reversal in ICH: Addition of rFVIIa

- 11-mo retrospective evaluation of all patients with warfarin-related ICH
- N=27 patients in a neurology/neurosurgery ICU
  - Group 1 (n=15): Vit K + FFP
  - Group 2 (n=12): Vit K + FFP + rFVIIa
- Median time to INR < 1.3 differed between groups
  - Group 1: 32.2 (10-72.8) hours
  - Group 2: 8.8 (1.8-130) hours
  - Slow INR decline in ESRD + rFVIIa (n=2, 110 & 130 hrs)

*P = 0.016


Off-Label rFVIIa: One Institution’s Process for Ensuring Best Practices

- Multidisciplinary group consensus
  - Surgery (trauma, neurosurg, CT), neurocritical care, hematology, anesthesia, blood bank, pharmacy, medicine, pediatrics
- FAHC Approved Indications
  - Blunt major trauma
  - Acute spontaneous ICH
  - Intra-operative major diffuse bleed
- rFVIIa order form for all off-label use

* None are FDA approved; All other indications necessitate hematology consult

Recommendations for rFVIIa* (1)

Patient must meet ALL of the following applicable criteria:
- Known coagulopathy or active bleeding
- Active bleeding with attempt at surgical control
- > 6 units PRBC infused in past 12 hrs
- Continued massive bleeding despite attempts at aggressive correction with blood products
  - Fibrinogen count > 100 mg/dL
  - Platelet count > 50,000
  - PT/INR ≤ 1.5x greater than normal

* Includes all off-label rFVIIa, not inclusive of only ICH patients

Recommendations for rFVIIa* (2)

Patient must meet ALL of the following applicable criteria:
- Continued massive bleeding & inability to correct coagulopathy or platelet deficiency despite aggressive transfusion support
  - > 8 units of FFP, 3 doses of platelets, 2 doses of cryoprecipitate within 4hrs
- Potential good outcome if bleeding ceases
- D/C of potentially contributory meds
- No current or hx of venous or arterial thrombotic event
- Trauma only: < 12hrs s/p injury and BD < 15
- ICH only: < 4 hours s/p onset & GCS > 5

* Includes all off-label rFVIIa, not inclusive of only ICH patients
Advantages of Implementing ICH Treatment Guidelines

- Minimize variability in prescribing
- Increase likelihood of positive outcomes
- Appropriate use based on clinical condition
- Pharmacists are uniquely poised to develop ICH treatment guidelines
  - Enhance use in population that may benefit most
  - Minimize use in population that has less propensity of benefit or heightened risk/benefit safety ratio
- Cost considerations

Rationale for Use of Thrombolysis in Intraventricular Hemorrhage (IVH)

- IVH occurs in 40% of ICH & worsens outcome
- Standard IVH therapy is drainage via external ventricular drain
  - EVD patency difficult to maintain due to occlusion from coagulated blood
- Blood degradation products from IVH → prolong ventricular enlargement & cause inflammation which impedes CSF absorption
- Thrombolytics may have advantageous role
  - Dissolve blood clot
  - Designed to supplement endogenous fibrinolysis activity
  - Reduce ICP
  - Clear deleterious blood breakdown products
  - Accelerate patient recovery
  - Decrease incidence of hydrocephalus
  - Improve overall patient outcome

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History of Thrombolytics in IVH

- Several case series report efficacy of intraventricular thrombolysis (urokinase / rt-PA)
- Few prospective, randomized data available
- Naff et al. → Prospective, MC pilot study (N=20)
  - Urokinase (< 25,000 IU q12h) vs. placebo
  - Increased 30-day survival in patients treated with intraventricular urokinase
  - Predicted mortality 58%, actual mortality 25%


Current Investigation of Thrombolytics in IVH

- Urokinase withdrawn from the market
- Intraventricular rt-PA more commonly used
- Current trial ongoing with rt-PA (CLEAR IVH)
  - rt-PA administered q8-12 hrs for several days until ventricles clear
  - Should be prepared with preservative-free saline
  - Drug is administered into ventriculostomy & clamped for at least 1 hr
  - CLEAR IVH- comparing 1 mg doses more frequently

Naff et al. Stroke 2000;31:841-7; Slide courtesy of D. Rhoney.

Minimally Invasive Surgery Plus rt-PA for ICH Evacuation (MISTIE)

- Local delivery of rt-PA into intracerebral hematoma
  - Several early case reports indicated use of stereotaxic surgery with hematoma aspiration offered improved outcome
  - MISTIE evaluating safety and ability to remove blood clot from brain tissue
    - Compare rt-PA to standard medical management
    - rt-PA-q8h dosing
    - PK analysis of hematoma aspirate
    - Study currently enrolling patients

Clinicaltrials.gov; Personal communication with D. Rhoney.

Intracerebral Hemorrhage Potential Future Investigations

- Minimally invasive surgery + thrombolysis
- Multi-modal therapy
  - Systemic hemostasis + local thrombolysis
- Glycemic control
- Temperature control / Hypothermia
- Stem cell therapies
- Modulators of immune response
Conclusions

• rFVIIa limits hematoma growth & improves functional outcome
  – Arterial thromboembolic events associated with rFVIIa are concerning (await FAST results)

• Thrombolytics for the subset of patients with IVH offer promise for future therapy

• Further medication-related modalities for treatment of ICH are desperately needed
References


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