Diagnosing & Treating Emergency Department CNS Hemorrhage Patients

E. Bradshaw Bunney, MD

Associate Professor
Department of Emergency Medicine
University of Illinois at Chicago
Our Lady of the Resurrection Medical Center
Chicago, IL

Global Objectives

- Improve pt outcome in CNS hemorrhage
- Know how to quickly evaluate stroke pts
- Know clinically how to use protocols
- Provide rationale ED use of therapies
- Facilitate useful disposition, documentation
- Improve Emergency Medicine practice

A Clinical Case

Clinical History

- 66 year old male presents with acute onset of aphasia and right sided weakness while eating at home
- Initially complained of a headache
- BP of 220/118 mm Hg
- Accucheck 316
- Initial GCS of 14

ED Presentation

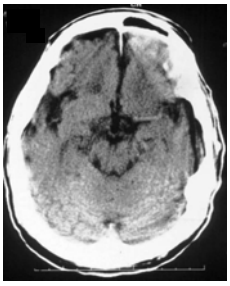
- ED VS
  - BP 224/124, P 100, RR 16, T 98.8, pulse ox 99%
- Somnolent, but slowly responds to simple commands
- Snores a bit when not stimulated
- Clear lungs and a regular cardiac rate and rhythm
- Neuro screening exam
  - Pupils midpoint, equal and reactive
  - L sided gaze preference
  - R facial weakness
  - R upper > lower extremity weakness
  - Expressive aphasia

Key Clinical Questions

- What are the key diagnostic issues?
- How can ED patient Rx be optimized?
- What guidelines direct our therapy?
- What drugs must be available for use?
- How can these drugs best be used?
- How should this ICH Rx be documented?

E. Bradshaw Bunney, MD

Which of these belong to this patient?




E. Bradshaw Bunney, MD

Ethnicity of ICH Risk

- Age and sex adjusted rate
  - U.S. 15 per 100,000
  - World wide 10-20 per 100,000
- Rates: 13.5 per 100,000 Caucasian
  38 per 100,000 African Americans
  55 per 100,000 Japanese

E. Bradshaw Bunney, MD

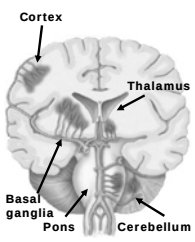
Primary Risk Factors

- Age
- Hypertension
- Alcohol intake
- Gender (M > F)
- Race
- Smoking
- Diabetes
- Vascular malformations
  - Moyamoya / aneurysms
- Infections
  - Vasculitis
  - Mycotic aneurysms
- Cerebral venous thrombosis
- Genetic
  - Apolipoprotein E ε4

E. Bradshaw Bunney, MD

Location

- Lobar
  - Associated with amyloid angiopathy
- Nonlobar
  - Due to hypertension
- Cerebellar
- Brain stem



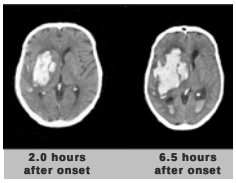
E. Bradshaw Bunney, MD

ICH is Dynamic

E. Bradshaw Bunney, MD

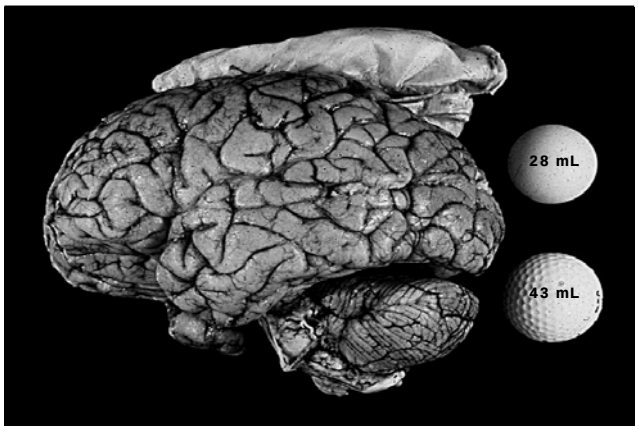
ICH Progression

- Symptoms often progress, associated with ICH growth
  - 2/3 with progression of symptoms
  - 1/3 maximal at onset
- Within hours from onset:
  - 26% with >33% growth in next 1º
  - 12% with >33% growth 1-20º



(Brott, *Stroke* 1997;28:1-5)

Size Matters



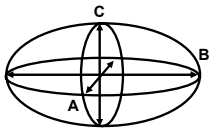
Prognosis

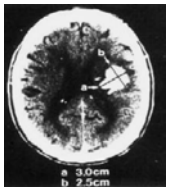
- Worse
  - Volume > 60 cm^3 and GCS < 9
    - 91% dead at 30 days
  - Patients with > 30 cm^3
    - 1 / 71 independent at 30 days
  - Other: age, seizures, intraventricular extension
- Better
  - Volume < 30 cm^3 and GCS 9 or higher
    - 19% dead at 30 days

(Broderick, *Stroke* 1993;24:987- 93)

Hematoma Volume

- Formula for volume of an ellipsoid
  - 4/3π (A/2)(B/2)(C/2)
  - Simplified A*B*C / 2





(Kothari, *Stroke* 1996;27:1304-5)

Medical Management
The Basics are Important

ICH Management

- Immediate stabilization (ABC's)
- Supportive medical care
  - Frequent comorbidities
- Neurologic specific care
- Hemorrhage specific interventions

E. Bradshaw Bunney, MD

Emergent Evaluation

- Baseline labs
  - CBC, coagulation parameters, electrolytes
- Neuroimaging
  - CT remains gold standard
    - Identify ICH and complications (hydrocephalus, herniation)
  - MRI / MRA
    - For structural abnormalities (AVM, aneurysms)
  - Angiography
    - Rarely emergently indicated, identifies vascular issues

E. Bradshaw Bunney, MD

Medical Management

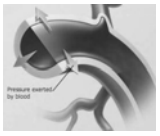
- ABC's
  - Maintain oxygen saturation ≥92%
  - Rapid sequence intubation
- Medical management
  - Prevention of hyperthermia (<37.5ºC)
  - Glycemic control
  - Coagulopathy correction (FFP, vitamin K)
  - No glycerol, corticosteroids, hemodilution
  - Secondary complication prevention

(EUSI, *Cerebrovasc Dis* 2003;16:311-318)

E. Bradshaw Bunney, MD

Medical Management is Important

Blood Pressure



E. Bradshaw Bunney, MD

Blood Pressure Management

- Hypertension very common
  - MAP > 140 in 34%, > 120 in 78%
  - Many 'normalize' over first 24 hours
- General goals
  - Maintain MAP < 130 mmHg with history of hypertension
  - Prevent hypotension (SBP < 90 mmHg)
  - Maintain:
    - Cerebral perfusion pressure (CPP=MAP-ICP) CPP > 70 mmHg
    - Central venous pressure from 5-12 mmHg
- Optimal blood pressure still to be determined

E. Bradshaw Bunney, MD

Blood Pressure Management

Common agents
- Labetalol
- Nicardipine
- Nitroprusside (theoretical risk of increasing ICP)

New data suggest SBP ≤ 150 mm Hg

Elevated blood pressure (some suggested medications)

Labetalol	5–100 mg/h by intermittent bolus doses of 10–40 mg or continuous drip (2–8 mg/min)
Esmolol	500 μg/kg as a load; maintenance use, 50–200 μg · kg^{-1} · min^{-1}
Nitroprusside	0.5–10 μg · kg^{-1} · min^{-1}
Hydralazine	10–20 mg Q 4–6 h
Enalapril	0.625–1.2 mg Q 6 h as needed

The following algorithm adapted from guidelines for antihypertensive therapy[68] in patients with acute stroke may be used in the first few hours of ICH (level of evidence V, grade C recommendation):

1. If *systolic* BP is >230 mm Hg or *diastolic* BP >140 mm Hg on 2 readings 5 minutes apart, institute nitroprusside.
2. If *systolic* BP is 180 to 230 mm Hg, *diastolic* BP 105 to 140 mm Hg, or mean arterial BP ≥130 mm Hg on 2 readings 20 minutes apart, institute intravenous labetalol, esmolol, enalapril, or other smaller doses of easily titratable intravenous medications such as diltiazem, lisinopril, or verapamil.
3. If systolic BP is <180 mm Hg and diastolic BP <105 mm Hg, defer antihypertensive therapy. Choice of medication depends on other medical contraindications (eg, avoid labetalol in patients with asthma).
4. If ICP monitoring is available, cerebral perfusion pressure should be kept at >70 mm Hg.

(Broderick, *Stroke* 1999;30(4):905-15)
(Ohwaki, *Stroke* 2004;35:1364-1367)

E. Bradshaw Bunney, MD

Medical Management is Important

Intracranial Pressure

E. Bradshaw Bunney, MD

Management of ICP

- Definition
  - ICP > 20 mm Hg for > 5 minutes
- Treatment goal
  - ICP < 20 mm Hg and CPP > 70 mm Hg
- Recommendations
  - ICP monitoring with GCS < 9
- Management
  - Patient positioning
  - Osmotherapy
  - Hyperventilation
  - Ventricular drainage

E. Bradshaw Bunney, MD

Management of ICP

- Head of bed at 45 degrees
- Osmotherapy
  - Mannitol 0.25-0.5 g/kg every 6 hours up to 5 days
  - Target mOsm $\leq$ 310 mmol/L
- Hyperventilation
  - Tidal volume of 12-15 ml/kg
  - Target pCO_2 30-35 mm Hg
- Neuromuscular paralysis
  - Nondepolarizing agents

(Broderick, *Stroke* 1999;30(4):905-15)

E. Bradshaw Bunney, MD

Medical Management is Important

Coagulation Correction

E. Bradshaw Bunney, MD

Coagulation Correction

- Warfarin
  - FFP 10 ml/kg
  - Vit K 10 mg IV over 10 mins
- Heparin (and some LMWH)
  - Correct with protamine 10 – 50 mg IVP over 1 – 3 mins
- Direct thrombin inhibitors
  - No antidote, consult hematology
- Platelet disorders
  - Correct with platelets (>100,000)
  - DDAVP 0.3 µg/kg IV over 30 mins

(MGH Stroke Service, 2005)

E. Bradshaw Bunney, MD

Warfarin Related ICH

- Use increases ICH risk 7-10 times
  - >10 fold risk if over 50 years of age
  - Increased risk dramatic if INR >4.0
    - 50-90% OAC-related ICHs occur while INR in the target range
  - ICH risk greatest at the start of treatment

Punthakee X et al. *Thrombosis Research* 2003;108:31-36.
Butler AC. Tate RC. *Blood Reviews* 1998;12:35-44
Winzen AR et al. *Ann Neurol* 1984;16:553-8.
Franke CL et al. *Stroke* 1990;21:726-30.
Hylek EM. Singer DE. *Ann Int Med* 1994;120(11):897-902.

E. Bradshaw Bunney, MD

Risk Factors for Warfarin Related ICH

- Advanced Age
- Hypertension
- Intensity of Anticoagulation
- Cerebral amyloid angiopathy

Hart RG. *Neurology* 2000:55:907-908.

E. Bradshaw Bunney, MD

Warfarin ICH Rx: Driving Principles

- Measure INR
- Establish the extent of INR elevation (< 5, 5-9, >9) and presence of bleeding
- Determine if an immediate neurosurgical intervention is needed
- Administer Vitamin K IV
- Order Coagulation Factor Replacement

E. Bradshaw Bunney, MD

Elevated INR Therapy: *The Procedure*

E. Bradshaw Bunney, MD

Elevated INR Rx Procedure

- Vitamin K 10 mg by slow IV infusion

E. Bradshaw Bunney, MD

Vitamin K

- Necessary to achieve more than a temporary reversal of anticoagulation
- Adequate response requires at least 2-6 and up to 24 hours
- Anaphylactic or anaphylactoid reactions rarely associated with IV administration
- Safest and most rapidly acting route of administration unclear

Wjasow C, McNamara R. *J Emerg Med* 2003;24(2):169-72.
Fiore LD et al. *J Thrombosis & Thrombolysis* 2001;11(2):175-83.

E. Bradshaw Bunney, MD

Coagulation Factor Replacement

- Options include
  - FFP
  - Prothrombin Complex Concentrates (PCC)
  - Recombinant Factor VIIa
- Normal coagulation achieved more rapidly with PCC and rFVIIa than with FFP

Fredriksson K et al. *Stroke* 1992;23:972-977.
Makris M et al. *Thromb Haemostasis* 1997;77:477-480.

E. Bradshaw Bunney, MD

Bedside Realities:
Can you answer these questions?

- Is thawed FFP immediately available from your blood bank?
- How long will it take your blood bank to get it to you?
- Does your hospital blood bank or inpatient pharmacy store PCC and rFVIIa?
- What is the relative rapidity of response of each of these agents?

E. Bradshaw Bunney, MD

Elevated INR Rx Procedure

- Vitamin K 10 mg by slow IV infusion
- Fresh frozen plasma (5-8 ml/kg, 1-2 units, 250-500 cc total)

E. Bradshaw Bunney, MD

Elevated INR Rx Procedure

- Vitamin K 10 mg by slow IV infusion
- Fresh frozen plasma (5-8 ml/kg, 1-2 units, 250-500 cc total)

  OR
- Prothrombin Complex Concentrate 25-50 IU/kg
  - Dose based on Factor IX units
  - Alternatively, 500 IU initially followed by second administration of 500 IU according to the INR value measured just after the first administration

E. Bradshaw Bunney, MD

Elevated INR Rx Procedure

- Vitamin K 10 mg subq or IVP
- Fresh frozen plasma (5-8 ml/kg)
  1-2 units, 250-500 cc total

  OR
- Prothrombin Complex Concentrate 25-50 IU/kg

  OR
- Recombinant Factor VIIa (40-60 µgr/kg)
  - Usually 3-4 mg total

E. Bradshaw Bunney, MD

PCC

- Prepared from pooled plasma of thousands of blood donors
  - Less viral transmission risk than FFP
- Contains vitamin K-dependent procoagulant and factors
- Infused over 15 minutes
- Relative thromboembolic risk unclear
- Acquisition cost of usual adult dose ≈ $450

Abe et al. *Rinsho to Kenkyu* [in Japanese] 1987;64:1327-37.
Sorensen B et al. *Blood Coagulation and Fibrinolysis* 2003:14:469-477.

E. Bradshaw Bunney, MD

Recombinant Factor VIIa

- Rapid onset of action
  - Almost immediate
    - Clinically apparent hemostasis within 10 minutes
- Short half life (2.3 hours)
- Relatively high acquisition cost
  - ≈ $2,500-$3,500 for 3-4 gm dose

Park p et al. *Neurosurgery* 2003;53:34-39.
Sorensen B et al. *Blood Coagulation and Fibrinolysis* 2003:14:469-477.
Novoseven [package insert]. Princeton, NJ: Novo Nordisk Pharmaceuticals, Inc; 2003.

E. Bradshaw Bunney, MD

FVIIa in Warfarin-Related ICH

- Freeman: 2004 Mayo Clin Proc
- Key Concept: Warfarin-related ICH can be treated successfully with rec FVIIa
- Data: 62 micrograms/kg Factor VIIa
- Data: INR decreased from 2.7 to 1.1
- Implications: This therapy used today as an adjunct to blood therapies in ICH patients whose bleed is INR-related

E. Bradshaw Bunney, MD

FVIIa Safety, Efficacy in ICH

- Mayer: 2005 NEJM
- Key Concept: FVIIa is safe when given within 3 hours of presentation
- Data: 399 pts, 3 doses, ICH growth, 90-day
- Data: Less ICH growth, improved outcome
- Data: Thrombo-embolic events noted
- Implications: Larger study is critical in order to establish clear benefit, safety

E. Bradshaw Bunney, MD

FVIIa Adverse Events

- O'Connell JAMA 2006; 295:293-298
- Adverse events reported to the FDA
- 1999-2004
- 431 reported, 185 thromboembolic
- 39 CVA, 34 MI, 32 PE, 26 art. Thrombus
- 52% occur in the first 24 hours
- Thromboembolic AE's follow off label use

E. Bradshaw Bunney, MD

Surgery in ICH

E. Bradshaw Bunney, MD

STITCH ICH Surgical Trial

- Mendelow: 2005 Lancet
- Key Concept: Surgery within 24 hours does not affect 6 month outcome
- Data: 25% of pts had a good outcome
- Data: Surgery did not change this rate
- Data: Surgery occurred after many hours
- Implications: Need to consider timely and selective neurosurgical intervention in order to impact outcome

E. Bradshaw Bunney, MD

ED Treatment and Patient Outcome

E. Bradshaw Bunney, MD

ED Patient Management

- The BP treated with IV labetalol
- The INR was noted to be 5.6
- Vitamin K administered
- 2 units FFP administered
- The pt was admitted to the neurosurgical ICU

E. Bradshaw Bunney, MD

Patient Outcome

- The hemorrhage size increased slightly on CT with slight intraventricular extension
- The patient's clinical condition slightly improved gradually
- Discharged to rehab 10 days after admission

E. Bradshaw Bunney, MD

Time Will Always Mean Brain!

- ICH continue to expand
- Early medical management essential
- Early coagulation correction critical (drip and ship)
- Hemostatic therapy may work best early

E. Bradshaw Bunney, MD

Questions??

www.ferne.org
ferne@ferne.org

E. Bradshaw Bunney, MD