Neuroresuscitation Research and Clinical Practice:

Surgical Trial in ICH (STICH): A Randomised Trial

EMRA /FERNE Neurological Emergencies Case Conference

Washington, DC
May 31, 2008

Edward Sloan, MD, MPH

Professor

Department of Emergency Medicine
University of Illinois College of Medicine
Chicago, IL

Attending Physician
Emergency Medicine

University of Illinois Hospital
Our Lady of the Resurrection Hospital

Chicago, IL

Disclosures

- President and Board Chair, Foundation for Education and Research in Neurologic Emergencies
- Stipend to the university for this work
- Honoraria provided for these lectures
- No individual financial disclosures

Global Objectives

- Improve pt outcome in ICH
- Know how to effectively Rx ICH patients
- Understand current guidelines
- Be aware of future therapies
- Improve Emergency Medicine practice

Session Objectives

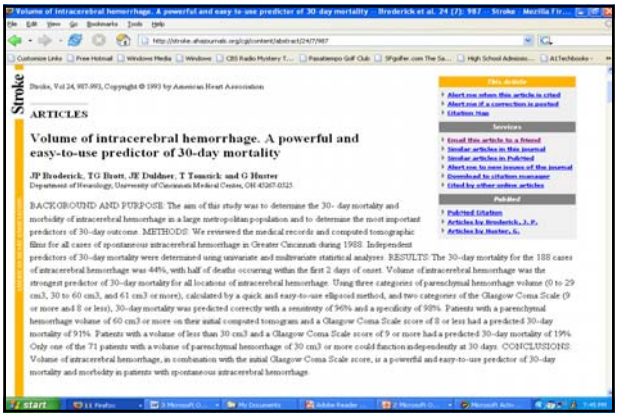
- Examine relevant ICH articles
- Discuss what these articles tell us
- Explore where each article will lead us
- Consider how EM practice might change

Edward P. Sloan, MD, MPH, FACEP

Methodology

- What was the purpose?
- What was the hypothesis?
- What was the data?
- What did the authors conclude?
- What limitations?
- What do we conclude?

Edward P. Sloan, MD, MPH, FACEP



Stroke

ARTICLES

Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality

JP Broderick, TG Brott, JE Duldner, T Tomsick, and G Huster

ICH Volume and Outcome

- Broderick: 1993 Stroke
- Key Concept: Hemorrhage volume and GCS predict 30 day mortality
- Data: 60 cc blood, GCS < 9, mort 91%
- Data: 30 cc blood, GCS > 8, mort 19%
- Implications: Simple ED observations allow for a reasonable outcome assessment

Edward P. Sloan, MD, MPH, FACEP

ICH Volume and Outcome

- Broderick: 1993 Stroke
- Data: 3 volumes, 2 GCS strata
- Data: 96% sensitivity, 98% specificity
- Data: 30+cc bleed, 1/71 independ at 30 d
- Implications: EM physicians can know likely outcome, allowing for realistic discussions with family & neurosurgeon

Edward P. Sloan, MD, MPH, FACEP

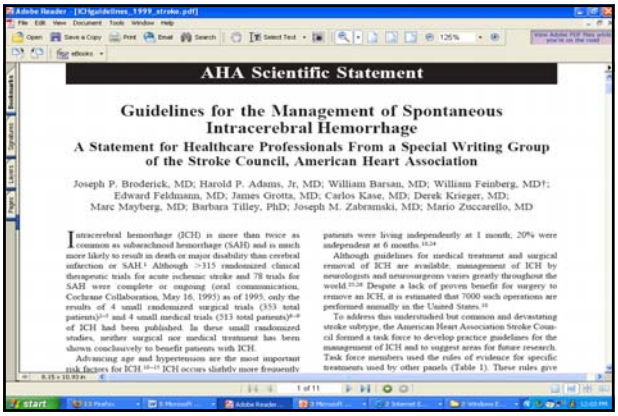
Early Hemorrhage Growth in Patients With Intracerebral Hemorrhage

Abstract

ICH Hemorrhage Growth

- Brott: 1997 Stroke
- Key Concept: ICH volume is dynamic, changes correlate clinically
- Data: 1 hr: 26% had 1/3 growth
- Data: 20 hr: another 12% had 33% growth
- Data: 1/3 growth = drop in NIHSS, GCS
- Implications: Efforts directed at stabilizing hemorrhage volume may impact patient outcome

Edward P. Sloan, MD, MPH, FACEP


AHA Scientific Statement

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

ICH Treatment Guidelines

- ASA Council: 1999 Stroke
- Key Concept: ICH guidelines exist
- Data: Detailed data on disease, epi
- Data: Specific recs on BP, ICP Rx
- Implications: This article will enhance the understanding of any EM physician on acute ICH patient management, make care consistent

Edward P. Sloan, MD, MPH, FACEP

ICH: Surgical Concepts

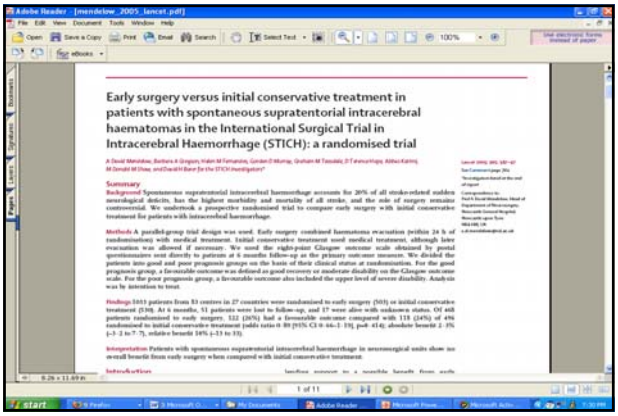
- Remember: Only 4 clinical trials!
- Total of 353 patients studied in all
- Remove clot, reduce pressure
- Manage brain trauma and edema
- Minimize trauma (superficial clots best)
- Minimally invasive approaches now used
- 75-100% mortality in surgical ICH trials

Edward P. Sloan, MD, MPH, FACEP

ICH: Surgical Indications

- Hard to specify…however…
- Cerebellar hemorrhage: 3 cm or larger or those that cause mass effect, compression
- ICH related to a surgical lesion
- Young patients who deteriorate
- Other indications less clear

Edward P. Sloan, MD, MPH, FACEP


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

STICH 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
- Implications: ED Rx becomes more important, given lower likelihood of operative neurosurgical intervention

Edward P. Sloan, MD, MPH, FACEP

STICH ICH Surgical Trial

- Mendelow: 2005 Lancet
- 1033 pts, non-US settings
- Data: early surgery vs. medical, surgical
- Data: Hemorrhage volume: 40 cc
- Data: 81% had GCS 9-15
- Data: Surgical time: 30 hrs, 60 hrs
- Data: Only 16% had surgery < 12 hrs

Edward P. Sloan, MD, MPH, FACEP

STICH ICH Surgical Trial

- Mendelow: 2005 Lancet
- Key concept: This study may not exactly tell the story of US practice
- May still need to consider operative intervention, will need to stabilize patients first

Edward P. Sloan, MD, MPH, FACEP

STICH: Rationale

- ICH 20% of all strokes
- Highest M & M
- Early surgery vs. initial conservative Rx
- Can the ischemic penumbra be preserved?
- Does early surgery fix elevated ICP and low CPP? (CPP = MAP – ICP)

Edward P. Sloan, MD, MPH, FACEP

STICH: Rationale

- Conflicting results from 9 trials
- No firm conclusions
- One meta-analyses included
- Non-randomised trials, one Japan study of 7000 patients
- Improved surgical techniques
- Will death and disability be reduced?

Edward P. Sloan, MD, MPH, FACEP

STICH: Methods

- 1995 study onset
- By 2003, 107 centers
- 1033 patients enrolled
- Consent obtained

Edward P. Sloan, MD, MPH, FACEP

STICH: Inclusion Criteria

- CT evidence of spontaneous ICH
- Within 72 hours of enrollment
- Neurosurgeon uncertain about best Rx
- Hematoma diameter of 2 cm
- GCS score > 4

Edward P. Sloan, MD, MPH, FACEP

STICH: Exclusion Criteria

- Aneurysm due to aneurysm or AVM
- Tumor due to tumor or trauma
- Cerebellar hemorrhage
- Brainstem extension
- Bad outcome likely
- Surgical not possible within 24 hours

Edward P. Sloan, MD, MPH, FACEP

STICH: Surgical Intervention

- Early surgery: in 24 hr of randomisation
- Late surgery: in setting of neurological deterioration
- Left to neurosurgeon discretion

Edward P. Sloan, MD, MPH, FACEP

STICH: Outcome Measures

- Death or disability using the extended Glasgow outcome scale at 6 months after ictus
- Resource use, length off stay

Edward P. Sloan, MD, MPH, FACEP

STICH: Sample Size Calculation

- Prospective sample of 259 patients
- 40% favourable outcome with conservative treatment
- Sample size 800 needed to show a 10% benefit from surgery
- 25% safety margin for protocol violations and crossovers
- Final sample size 1000

Edward P. Sloan, MD, MPH, FACEP

STICH: Statistical Analysis

- Intention-to-treat analysis
- Favourable vs. unfavourable analysis
- Prognosis estimated from formula: Prognostic score = (10 x GCS) – age – (.64 x ICH volume)
- This lead to a way to define outcome

Edward P. Sloan, MD, MPH, FACEP

STICH: Defining Outcome

- Predicted good prognosis: good outcome was good outcome or moderate disability
- Predicted poor prognosis: good outcome was good outcome, moderate disability, or upper severe disability categories
- *Did they do better than expected?*

Edward P. Sloan, MD, MPH, FACEP

STICH: Defined Subset Analyses

- Age 65 cutoff
- Haematoma volume 50 cc cutoff
- GCS score < 9, 9 to 12, or 13+
- Lobar vs. basal ganglia/thalamic
- Presence of thrombolytic therapy
- Neurological deficit
- Craniotomy vs. other

Edward P. Sloan, MD, MPH, FACEP

STICH: Population

- 1033 patients from 83 centres in 27 countries
- 503 early surgery
- 530 to initial conservative
- Well matched at baseline

Edward P. Sloan, MD, MPH, FACEP

STICH: Characteristics

- Median age 62 years
- Time to randomisation: 20 hour median
- 20% comatose
- 40% GCS 13+
- 40% lobar hemorrhage, 40% BG/T
- Median volume 38 cc, at 1 cm depth
- *Time to OR = 30 and 60 hours*

Edward P. Sloan, MD, MPH, FACEP

STICH: Surgery

- 6% of early surgery pts received operative intervention after 24 hours
- 26% of conservative patients received operative intervention, usually due to rebleeding or deterioration
- Deterioration usually 3 + GCS points
- Superficial, lobar hemorhhages to OR

Edward P. Sloan, MD, MPH, FACEP

STICH: Main Result

- Prognosis-based dichotomy
- Early surgery: 26% favorable outcome
- Conservative: 22% favorable outcome
- OR = 0.89, ns
- Early surgery 2.3% absolute benefit, 10% relative benefit
- Mortality 36, 37% in the two groups

Edward P. Sloan, MD, MPH, FACEP

STICH: Other Results

- 8% surgery benefit if haematoma less than one cm from surface
- 6% surgery benefit if haematoma evacuated by craniotomy
- If coma, then bad outcome.
- Early surgery in coma patients increased bad outcome risk by 8%

Edward P. Sloan, MD, MPH, FACEP

STICH: Other Results

- Cost analysis, limited numbers
- No clear significant differences
- (Data difficult to digest)

Edward P. Sloan, MD, MPH, FACEP

STICH: Discussion

- Favorable outcome based on prognosis-based indices do not differ
- These trials are hard to conduct and will be harder in the future
- Prognosis-based outcome made it possible to detect more modest amounts of benefit

Edward P. Sloan, MD, MPH, FACEP

STICH: Discussion

- "However, we still cannot give a definitive answer to the questions: can a policy of early surgical intervention for patients with ICH be recommended, and, if so, under what conditions?"

Edward P. Sloan, MD, MPH, FACEP

STICH: Limitations

- Bias in ransomisation
- Outcome measure not blinded
- Subgroup analysis uses up statistical power

- Who wan't enrolled and why?
- What happened to these patients?

Edward P. Sloan, MD, MPH, FACEP

STICH: Coma Patient Results

- Uniformly bad outcome
- Surgery is probably harmful
- 40 operations for one good outcome

Edward P. Sloan, MD, MPH, FACEP

STICH: Final Conclusions

- Analyze in context of all trials results
- Can't recommend surgery
- Surgeons should do more studies

Edward P. Sloan, MD, MPH, FACEP

STICH: Some Issues

- Intervention by group a problem
- Time to surgery a problem
- This may not reflect US paradigm

Edward P. Sloan, MD, MPH, FACEP

STICH: Baseline Differences

- The surgical patients differed at baseline in the two groups
- Page 391
- Table 3
- Early surgical patients: less sick
- Conservative patients who received operative: more sick

Edward P. Sloan, MD, MPH, FACEP

STICH: Conclusions

- Study might have concluded: Better than expected outcomes don't occur with or without surgical intervention in ICH patients who are treated many hours after the ictus and who receive delayed operative intervention, often after deterioration

Edward P. Sloan, MD, MPH, FACEP

STICH: What is the Problem?

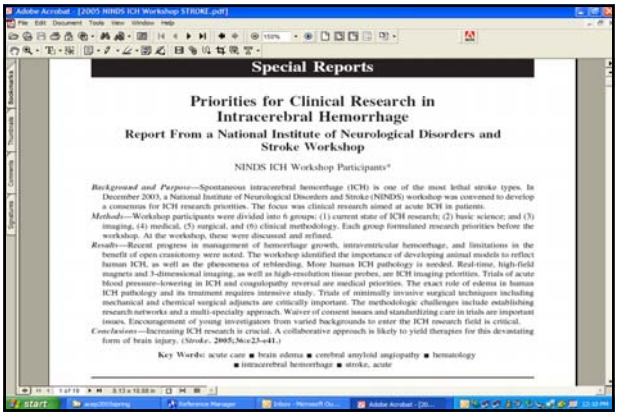
- Generalising the results to a different patient population or treatment paradigm may lead to changes in management that are not indicated
- We should continue to consider operative intervetion, given US differences and the conflicting publications, of which this is one

Edward P. Sloan, MD, MPH, FACEP

STICH: What Have We Learned?

- Surgery may not be beneficial in ICH
- Comatose patients (especially those with a large hemorrhage) do poorly and may not warrant surgical intervention
- Superficial hemaetomas may benefit from surgical intervention
- Research is hard to do
- We have more to do and learn

Edward P. Sloan, MD, MPH, FACEP



Special Reports

Priorities for Clinical Research in Intracerebral Hemorrhage

Report From a National Institute of Neurological Disorders and Stroke Workshop

NINDS ICH Workshop Participants*

Background and Purpose—Spontaneous intracerebral hemorrhage (ICH) is one of the most lethal stroke types. In December 2003, a National Institute of Neurological Disorders and Stroke (NINDS) workshop was convened to develop a consensus for ICH research priorities. The focus was clinical research aimed at acute ICH in patients.

Methods—Workshop participants were divided into 6 groups: (1) current state of ICH research; (2) basic science; and (3) imaging, (4) medical, (5) surgical, and (6) clinical methodology. Each group formulated research priorities before the workshop. At the workshop, these were discussed and refined.

Results—Recent progress in management of hemorrhage growth, intraventricular hemorrhage, and limitations in the benefit of open craniotomy were noted. The workshop identified the importance of developing animal models to reflect human ICH, as well as the phenomena of rebleeding. More human ICH pathology is needed. Real-time, high-field magnets and 3-dimensional imaging, as well as high-resolution tissue probes, are ICH imaging priorities. Trials of acute blood pressure–lowering in ICH and coagulopathy reversal are medical priorities. The exact role of edema in human ICH pathology and its treatment requires intensive study. Trials of minimally invasive surgical techniques including mechanical and chemical surgical adjuncts are critically important. The methodologic challenges include establishing research networks and a multi-specialty approach. Waiver of consent issues and standardizing care in trials are important issues. Encouragement of young investigators from varied backgrounds to enter the ICH research field is critical.

Conclusions—Increasing ICH research is crucial. A collaborative approach is likely to yield therapies for this devastating form of brain injury. (*Stroke*. 2005;36:e23-e41.)

Key Words: acute care ■ brain edema ■ cerebral amyloid angiopathy ■ hematology ■ intracerebral hemorrhage ■ stroke, acute

NINDS ICH Research Agenda

- NINDS Workshop: 2005 Stroke
- Key Concept: Fundamental questions Re: ICH treatment and research
- Data: Critical medical, surgical issues
- Data: Extensive info regarding acute Rx
- Implications: Although much theoretical info, an important source of facts that will enhance current clinical practice

Edward P. Sloan, MD, MPH, FACEP

NINDS ICH Research Agenda

- NINDS Workshop: 2005 Stroke
- Key Concept: Landmark article
- Data: 6 writing groups
- Data: 226 references
- Implications: A must for any educator or clinician who wishes to know more about the optimal ED Rx of ICH patients

Edward P. Sloan, MD, MPH, FACEP

Key Learning Points

- Research is a tough business, as is treating ICH patients in the ED
- If the ICH is large and the pt comatose, plan no operative intervention
- In the US, early immediate operative intervention is still an option for smaller, superficial bleeds, especially in viable patients who are not comatose
- We must know how to talk the talk with our neurosurgical consultants
- More work is to be done

Edward P. Sloan, MD, MPH, FACEP

Questions??

www.ferne.org
ferne@ferne.org

Edward P. Sloan, MD, MPH
edsloan@uic.edu
312 413 7490

ferne_emra_2008_neuro_conf_saem_sloan_ich_053108_final
7/22/2008 2:11 PM

Edward P. Sloan, MD, MPH, FACEP