Acute Injury Phase Clinical Trials in Acute Traumatic Brain Injury

Past Failures and Future Prospects

Robert D. Welch, MD, MS
Department of Emergency Medicine
WSU School of Medicine

Should be titled:

FRUSTRATIONS IN EXPERIMENTAL DESIGNS

Goals

- Discuss failures and problems with past studies
- Review some current clinical trials related to TBI
  - ProTECT
  - INTREPID
- Consider other methods of evaluating new therapies

Disclosure

- **Neurological Emergencies Treatment Trials Network (NETT) Clinical Site Hubs** (Principal Investigator)
  - Funding Source: National Institutes of Health, NINDS (2 U10 NS059012-06)
  - Role: Program Director
- **ProTECT™ III (Progesterone for the Treatment of Traumatic Brain Injury** (David Wright, MD – PI)
  - Funding Source: NIH (NINDS)
  - Role: Site PI
- **ALERT- ATO-06: A Prospective Clinical Evaluation of Biomarkers of Traumatic Brain Injury**(Ronald Hayes, PI)
  - Funding Source: DOD via Banyan Biomarkers
  - Role: Site PI

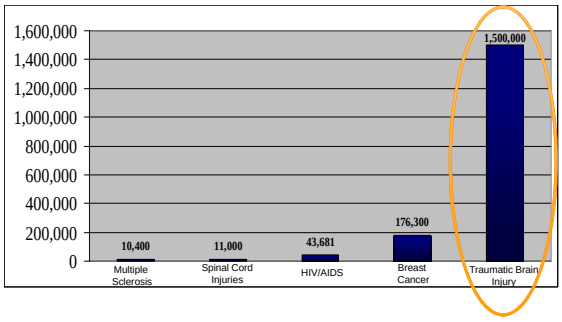
Disclosure (cont.)

- **INTREPID-2566 Study (INvestigating TREatments for the Prevention of secondary Injury and Disability following TBI**
  (A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study of NNZ-2566 in Patients with Traumatic Brain Injury (TBI)
  - Funding Source: DOD via Neuren Pharmaceuticals
  - Role: Site sub-Investigator

Requisite Review

- Scope of TBI
  - 1.4 million suffer TBI each year
  - 1.1 million treated and released from EDs
  - > 235,000 hospitalized
  - > 50,000 die
  - Many more are permanently disabled (80,000 to 90,000?)
- Progressive Mortality Reduction over 30 yrs.
  - 50%
  - 35%
  - 25%
  - Even lower (guidelines?)

Comparison of Annual Incidence



From Brain Trauma Foundation Website

- Traumatic Brain Injury (TBI) is the leading cause of death and disability in children and adults from ages 1 to 44.
- Brain injuries are most often caused by motor vehicle crashes, sports injuries, or simple falls on the playground, at work or in the home.
- Every year, approximately 52,000 deaths occur from traumatic brain injury.
- An estimated 1.5 million head injuries occur every year in the United States emergency rooms. [a]
- An estimated 1.6 million to 3.8 million sports-related TBIs occur each year.
- At least 5.3 million Americans, 2% of the U.S. population, currently live with disabilities resulting from TBI.
- Moderate & severe head injury (respectively) is associated with a 2.3 and 4.5 times increased risk of Alzheimer's disease.
- Males are about twice as likely as females to experience a TBI.
- The leading causes of TBI are falls, motor vehicle crashes, struck by or against events, and assaults, respectively.
- TBI hospitalization rates have increased from 79% per 100,000 in 2002 to 87.9% per 100,000 in 2003.
- Exposures to blasts are a leading cause of TBI among active duty military personnel in war zones.
- Veterans' advocates believe that between 10 and 20% of Iraq veterans, or 150,000 and 300,000 service members have some level of TBI.
- 30% of soldiers admitted to Walter Reed Army Medical Center have been diagnosed as having had a TBI.

Injuries to Fatalities Ratio

(requiring professional medical assistance)

- Football = 65,000 injuries/fatality
- Golf = 33,000

Injuries to Fatalities Ratio

(requiring professional medical assistance)

- Sailing = 200

Injuries to Fatalities Ratio

(requiring professional medical assistance)

- Caving/Rock Climbing = 16

Injuries to Fatalities Ratio

(requiring professional medical assistance)

- Aviation = 2

Other Possible Reasons

- Rise in severe TBI among the elderly
- Poor use of restraining devices in MVC
- Endotracheal intubation in the field and ICP monitoring (both may increase mortality?)
- Patient selection for aggressive treatment
- Data published from centers in which mortality is relatively high (newer data)
  - Level II or low-volume hospitals
  - Developing countries

THERAPEUTIC TRIALS

WHERE DO WE STAND???

20 compounds in 50 TBI trials over 30 years—all failed (early 2000)

- Majority of these were directed at the secondary injury cascade
- Enhance brain remodeling (Neuro-restoration) is an area that is promising

Examples of Failed Therapies

- Magnesium Sulfate
- Dexanabinol
- Tirilizad
- PEG-SOD
- Methylprednisolone

- Non-Pharmacological
  - Hypothermia ?
  - Decompressive Crainectomy ?

Level of Evidence

- Level I
  - Good quality RCT
  - Standard of care
  - Must do stuff (standard)
- Level II
  - Moderate RCT, good cohort or case-control
  - Should do in most cases (guideline)
- Level III
  - Poor RCT, mod/poor cohort/case-control, case series
  - Can do (optional ???)

Steroids

- "The use of steroids is not recommended for improving outcome or reducing intracranial pressure (ICP). In patients with moderate or severe traumatic brain injury (TBI), high-dose methylprednisolone is associated with increased mortality and is contraindicated."
- OUR ONLY LEVEL I recommendation!
- Issues: Little emphasis on re-examining steroid use!

RCTs

- RCTs are currently the most rigorous method to determine if there is a cause–effect relation between potential new treatment and clinically relevant outcomes
- RCTs are of higher quality and provide quality evidence by avoiding common past pitfalls and problems with study design and implimentation

Pitfalls

- "unclear hypotheses and multiple objectives"
- "poor selection of endpoints"
- "inappropriate subject selection criteria"
- "non-clinically relevant or feasible treatment intervention regimens"
- "inadequate randomisation, stratification, blinding"
- "lack of stratification in small RCTs"
- "inadequate blinding of trials"
- "insufficient sample size/power"
- "failure to use intention to treat analysis"
- "failure to anticipate common practical problems encountered during the conduct of a RCT"

Other possibilities

- Heterogeneity of TBI (it's not one injury)
- Some drugs may just not work in the human environment
- Risk/Benefit profile

Twelfth Medical Research Council Acute myeloid Leukemia Trial

- Question: Would an additional 5th course of therapy confer additional benefit compared to the established 4 course treatment.
- November 1994 to May 2002
- Target sample size 1000 to have 90% power to detect a 20% proportional improvement (50% to 60%, 10% absolute, for $p<0.05$, two-tailed).

Monitoring

- Annually or more frequently if requested
- DMEC = Data monitoring and ethics committee (their version of DSMB).
- No fixed stopping rules

Interim Analyses

- March 1998
  - 340 patients up to July 1997
  - HR 0.47 (0.29 – 0.77, p=0.003) in favor of 5 course therapy
- Decided not to stop and requested an additional report at 6 (opposed to 12) months
- September 1998 HR 0.55 (0.38 – 0.80, p=0.002)

Trial not Stopped

- March 1998 – 53% reduction
  September 1998 – 45% reduction
- Treatment effect was much greater than what was plausibly anticipated for 1 additional course of therapy
- Follow-up was short

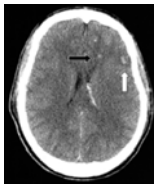
Variability of Outcomes

- 58 y.o. male middle-school teacher
- Harley-Davidson Motorcycle accident
- GSC = 8 on arrival
  - Subdural, Contusion, and Traumatic SAH
  - Fractured right humerus and pelvis
  - Pulmonary contusions
- 1 month ICU and step-down unit care
- Inpatient/outpatient rehab
- Back teaching 9 in months

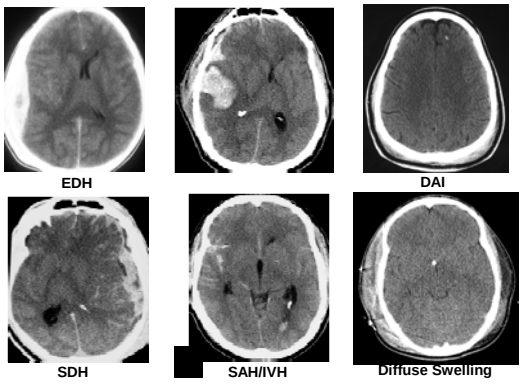
What's the difference???

Variability of Outcomes

- 28 y.o. male restaurant worker
- MCV – unrestrained driver
- GCS = 9 on arrival
  - Small hemorrhages
  - DAI
  - No other significant injuries
- Neurological ICU for 5 days
- Prolonged inpatient rehab
- Persistent neurological and cognitive deficits



Examples of Severe TBI



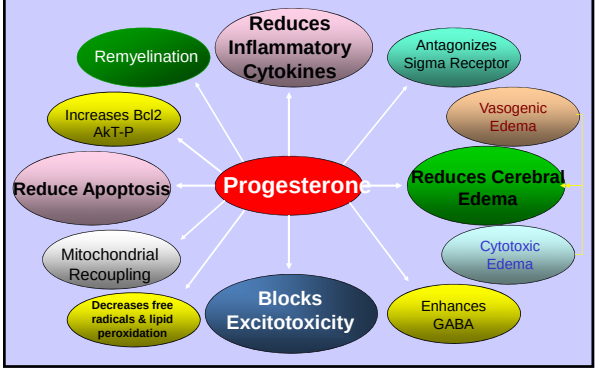
At Present There Are No Effective Drug Treatments For Traumatic Brain Injury

What Next?

Corroborative Research

- Over 100 publications showing positive results with progesterone in neurological injury
- 24 different labs
- 4 animal species
- 22 different animal models

Potential mechanisms in TBI



Proposed Mechanisms

- Inhibits apoptosis by
  - Reducing:
    - Release cytochrome c
    - Levels of B-cell lymphoma (Bcl)-2-associated X protein (Bax)
    - Levels of Bcl-2-assocaited death promotor (BAD)
    - Levels of Caspase-3
  - Up-regulates expression of anti-apoptotic mitochondrial proteins such as Bcl-2
- Reverses alteration in mitochondrial respiration
- Normalize expression of Na/K ATPase
- Reduces Inflammation
  - microglial activation
  - inflammatory cytokines
    - TNF-α, IL-1, p65, others …

Progesterone Mechanisms (cont.)

- Reduces lipid peroxidation
  - Up-regulate superoxide dismutase and other antioxidants
  - Result is stabilizing membranes and maintaining BBB
- Regulates expression of auquaporin-4 in astrocytes – may help reduce edema
- Reduces exitotocicity at NMDA receptors
- Increased GABA receptor release of inhibitory neurotransmitters (decreased seizures)
- May need adequate vitamin D stores for anti-inflammatory effect

Clinical Trials

- Two phase II trials suggest benefit
- NIH funded ProTECT^{TM} III trial – PI: David Wright, MD

Progesterone for TBI, Experimental Clinical Treatment

ProTECT™

A Phase IIa, double-blind, placebo-controlled randomized clinical trial

- Blunt mechanism TBI
- Moderate (iGCS 9-12) to severe (iGCS 4-8) injury
- Age ≥18 yrs
- 4:1 block randomization (Rx versus placebo)
- Goal: enroll 100 subjects

MARK TWAIN

- "It is amazing what little harm doctors do when one considers all the opportunity they have".

Safety

- No drug-related adverse cardiac, respiratory, coagulopathic or immunologic effects
- With the exception of 30 day mortality, no difference in the frequency or rate of AEs or SAEs between treatment vs. placebo groups

ProTECT™ III

- Progesterone for the Treatment of Traumatic Brain Injury
- Phase 3 clinical trial
- Can enroll under the EFIC regulation

Primary Objective

- Determine the efficacy of administering intravenous (IV) progesterone (initiated within 4 hours of injury and administered for 72 hours, followed by an additional 24 hour taper) versus placebo for treating victims of moderate to severe acute TBI (Glasgow coma scale score 12-4).

Primary Hypothesis

- Progesterone will increase the proportion of patients with a favorable outcome by a 10% (absolute) difference, determined by the Glasgow Outcome Scale-Extended (GOSE) score at 6 months post injury when compared to placebo.
- Secondary Outcomes: Examine the efficacy of IV progesterone vs. placebo for treating patients with moderate to severe acute TBI on additional 6 month outcomes: Mortality, Disability Rating Scale (DRS), cognitive, neurological and functional outcomes using a select battery of tests, and rates of adverse and serious adverse events.

Inclusion Criteria

- Moderate to severe brain injury (iGCS 4 – 12 or motor response 2-5, if intubated)
- Age >18 years
- Blunt, traumatic, closed head injury
- Able to initiate study drug infusion within 4 hours from time of injury

Exclusion Criteria

- Non-survivable injury as determined by treating team
- Bilateral dilated unresponsive pupils
- Spinal cord injury with neurological deficits
- Cardiopulmonary arrest
- Status epilepticus on arrival
- SBP < 90 for two consecutive readings at least 5 minutes apart anytime prior to randomization
- O2 Sat < 90 for at least 5 consecutive minutes anytime prior to randomization
- Prisoner or ward of state
- Known active breast or reproductive organ cancers (via medical records or family interview)
- Known allergy to progesterone or Intralipid components (egg yolk) (via medical records or family interview)
- Known history of blood clotting disorder (Protein S or C deficiency, etc.) or pulmonary embolism (via medical
- records or family interview)
- Blood or serum ethanol (EtOH) > 250 mg %
- Positive qualitative urine or serum pregnancy test

Methods

- Double Blind (Masked) Placebo Controlled
- Sample Size:
  - Power 85% to detect a 10% absolute difference in outcomes between treatment groups at the two-sided α of 0.05.
    - 462 subjects per group if expected favorable outcome is 50% in those receiving placebo and 60% in those given treatment
    - 3 analyses (2 interim after approximately 33% and 67% of enrollment and 1 final using O'Brien Fleming boundaries)
    - Non-adherence rate of 10% (withdrawal of consent and loss to follow-up)
- The total sample size is 1140 subjects

Primary Outcome

- GOSE at 6 months
- Eight-point ordinal scale, with higher scores associated with better outcome:
  - 1 = "death"
  - 2 = "persistent vegetative state"
  - 3 - 4 = "severely disabled"
  - 5 - 6 = "moderately disabled"
  - 7 - 8 = "good recovery"

Favorable vs non-Favorable

- Patients with the most severe injury (iGCS 4-5) will have a favorable outcome if the GOSE is good to severe
- Patients with an intermediate severe injury (iGCS 6-8) will have a favorable outcome if the GOSE is good to moderate
- Patients with a moderate injury (iGCS 9-12) will have a favorable outcome if the GOSE is good recovery

Analysis

- Intention-to-treat
- Proportion of subjects with favorable outcome 6 months post randomization
- The primary efficacy hypothesis is tested via generalized linear model relating the probability of a favorable outcome to the treatment, adjusting for three covariates (injury severity, gender, and age)

Clinical Standardization Guidelines

- Supported by: National Institute for Neurological Disorders and Stroke
- TEMPLATE for the care of patients at sites participating in the multicenter clinical trial ProTECT™ III
- ProTECT™ III Clinical Standardization Team:
  - Geoff Manley, MD, PhD – Neurosurgery, University of California, San Francisco, (Chairman)
  - Bizhan Aarabi, MD – Neurosurgery, University of Maryland
  - Odette Harris, MD, MPH - Neurosurgery, Stanford
  - Claude Hemphill, MD – NeuroIntensivist, UCSF
  - Peter LeRoux, MD – Neurosurgery, University of Pennsylvania
  - Lisa H. Merck, MD, MPH – Emergency Medicine, Emory University
  - Raj Narayan, MD - Neurosurgery, University of Cincinnati
  - David O. Okonkwo, MD, PhD - Neurosurgery, University of Pittsburgh
  - Jose Pascual MD, PhD - Trauma Surgery and Critical Care, University of Pennsylvania
  - Jeff Salomone, MD – Trauma Surgery and Critical Care, Grady Memorial Hospital, Atlanta, GA
  - William Schwab, MD – Trauma Surgery and Critical Care, University of Pennsylvania
  - Alex Valadka, MD – Neurosurgery, Seton Brain and Spine Institute, Austin, Texas
  - David W. Wright, MD - Emergency Medicine, Emory University

SyNAPSe trial

INTREPID (Neuren)

- A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study of NNZ-2566 in Patients with Traumatic Brain Injury (TBI)
- Multicenter, double-blind, placebo-controlled
  - Randomized 2:1 for active versus placebo
  - safety, dose-escalation, pharmacokinetic and efficacy study of 20 mg/kg i.v bolus infusion of NNZ-2566 over 10 minutes followed by:
    - 1 mg/kg/h (Cohort 1, n=20)
    - 3 mg/kg/h (Cohort 2, n=20)
    - 6 mg/kg/h (Cohort 3, n=133) intravenous infusion for a total of 72 consecutive hours

Other Drug Therapies Under Investigation

- Minocycline
- ILGF-1 analogues
- Citicoline
- Cyclosporin A
- Erythropoetin
- Conivaptan
- Hyperbaric oxygen
- Statins
- Nitric Oxide
- Many others

I Think This Research Stuff is Important to Know BUT…..

Engineers and scientists will never make as much money as business executives. The following simple mathematical proof explains why this is true.

- Postulate 1 : Knowledge is power
- Postulate 2 : Time is money

As every scientist knows

$$\frac{Work}{Time} = Power$$

Since:
Knowledge = Power
Time = Money

$$\frac{Work}{Money} = Knowledge$$

Solving for Money

$$\frac{Work}{Knowledge} = Money$$

Thus, as knowledge approaches zero, money approaches infinity regardless of the work done.

Conclusion: The less you know, the more you make!!!

Decompressive Craniectomy

- DECRA Trial
- RESCUEicp (started Jan 2004)
  - 366 patients as of June 1, 2013 (n total=400)
  - Higher ICP threshold
    - 25 mm Hg (rather than 20 mm Hg)
    - Duration of 1 to 12 hours (rather than 15 minutes)
  - Evacuation of a hematoma allowed before randomization
  - Permitted surgical techniques (bifrontal or unilateral wide decompression)

DECRA

- Of 3478 patients for eligibility, only 155 were enrolled
  - Dec 2002 – April 2010)
  - 73 - early decompressive craniectomy
  - 82 - standard care
  - Baseline characteristics similar except fewer with reactive pupils in craniectomy group
- Fifteen patients (18%) in the standard-care group crossed over

DECRA Results – GOSE at 6 months

- Worse functional outcome in the craniectomy group (OR = 1.84; 95% CI 1.05 to 3.24)
- After adjustment for pre-specified covariates (OR = 1.66; 95% CI, 0.94 to 2.94; P = 0.08)
- Post hoc adjustment for pupil reactivity (1.53; 95% CI, 0.86 to 2.73; P = 0.15)
- Unfavorable outcome (death, vegetative state, or severe disability) higher in treatment group
- Mortality similar

What Next?

- Hypothermia for elevated ICP
- More selective craniectomy for elevated ICP

Comparative Effectiveness Research

Not Efficacy Trial Designs

Non-experimental Designs

Summary

- Still no proven neuroprotective therapy
- Things that “seem to work” have not been proven
- Would like to say Progesterone will work but…
- Laboratory studies must do better to bring more realistic therapies to the human world
- Re-think our approach to studying clinical application of new therapies

Thanks