SIH: Trials and Research Endeavors

Tim Amrhein, MD
Assistant Professor of Neuroradiology
Duke University Medical Center
@TimAmrheinMD
Disclosures

• No relevant disclosures
• RSNA Research Scholar Grant
• ASNR Comparative Effectiveness Award
• NIH R01
Objectives

• Getting from here to there
• Types of research
• What is good research?
• Where are we now?
• Where are we going?
Getting From Here to There
Getting From Here to There

- Myocardial Infarction
  - 1912 (JAMA): “wound of heart”
    - physical and emotional rest
    - quiet isolation in bed 6 wks

Herrick JB. JAMA 1912; 59: 2015–20
Getting From Here to There

• Myocardial Infarction
  – 1912 (JAMA): “wound of heart”
    • physical and emotional rest
    • quiet isolation in bed 6 wks
  – 2018 (JAMA): myocardial reperfusion
    • ECG, blood markers, echo, medications (thrombolytics), cath lab, stenting, ICU

Ibanez et al Eur Heart Journal; 39(2):119-177
General Research Goals

- Create *generalizable* knowledge
- Determine: best treatments, causation, prevalence of disease
Types of Research
Expert Opinion

• Statements of opinion from thought leader
  – Can say whatever they want

• Claim’s validity based on *person* making claim rather than *evidence*

• Conflicts of interest
  – industry / financial, personal

• Bias: based on single person’s experience
  – limited in scope
Expert Opinion

- Miasma theory of disease
  - cholera, chlamydia, plague
  - caused by “bad air” or pollution

- 1880: germ theory
Case Series

- Report one or multiple patients with same disease or treatment

**PROS**
- Describes characteristics
- Easy, Low cost, Less time
- Generate hypothesis

**CONS**
- No control or comparison group
- Information bias
- Selection bias
Case Series

- Report one or multiple patients with same disease or treatment

CONS
- No control or comparison group
- Information bias
- Selection bias
Case Series

- Report one or multiple patients with same disease or treatment

**PROS**
- Describes characteristics
- Easy, Low cost, Less time
- Generate hypothesis

**CONS**
- No control or comparison group
- Information bias
- Selection bias

**Useful for:**
- Reporting sentinel events: toxicity of therapy, recognition of epidemics, initial identification of new disease
Case Control

- Retrospective

- Two groups:
  - Case: group of subjects with disease
  - Control: similar group of subjects without disease

- Look for differences in predictors of disease
  - (e.g. smoking in lung cancer)

- Odds Ratio: relative risk of developing disease
Case Control

Example: SIH in Ehlers-Danlos (made up numbers)
- 0.16% incidence SIH in non-EDS
- assume relative risk 50
- 80% power
- 6000 patients cohort or RCT
  - multiple years follow
- 16 each group for case-control
Case Control

**PROS**
- Efficiency for rare diseases
- Relatively easy and low cost
- Generate hypothesis

**CONS**
- Only one outcome studied
- Cannot estimate prevalence
Case Control

**PROS**
- Efficiency for rare diseases
- Relatively easy and low cost
- Generate hypothesis

**CONS**
- Only one outcome studied
- Cannot estimate prevalence
- Sampling bias
- Retrospective measurement bias
Cohort Studies

• Longitudinal studies:
  – patient group assembled at beginning
  – repeated data acquired over time in same patients

• Only observing, no active intervention

• Retrospective or prospective

• Two purposes: descriptive and analytic

• Can suffer from confounding
Randomized Controlled Trials (RCT)

- Prospective
- “Experimental”: active intervention
- Patients are randomly assigned to arms of study
- Eliminates confounding and reduces bias
- Gold standard
- Difficult, time consuming, expensive
What is “good” research?

How to avoid “fake news”
Levels of Evidence

I: RCT
II: Cohort
III: Case Control
IV: Case Series
V: Expert Opinion

Sacket DL et al How to Practice and Teach EBM
Where are we now?
Past Research

Publications

<table>
<thead>
<tr>
<th></th>
<th>1916</th>
<th>1960</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SIH

<table>
<thead>
<tr>
<th></th>
<th>1916</th>
<th>1960</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1990
Past Research

**Publications**

<table>
<thead>
<tr>
<th>Year</th>
<th>MI</th>
<th>SIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1916</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2018</td>
<td>9000</td>
<td>160</td>
</tr>
</tbody>
</table>

**SIH**

<table>
<thead>
<tr>
<th>Year</th>
<th>1960</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>150</td>
</tr>
<tr>
<td>2018</td>
<td>200</td>
</tr>
</tbody>
</table>
Past Research
Expert Opinion

Off label use of Gd in CSF space
May be helpful to find slow leaks and CVF
Unsure of risks
Advocates for its use in selected cases
Expert Opinion

Intrathecal Gadolinium for Magnetic Resonance Myelography in Spontaneous Intracranial Hypotension: Valuable But May Be Risky

Dimitrios Parissis, PhD
Panos Ioannidis, PhD
Dimitrios Karacostas, PhD

JAMA Neurology  June 2014  Volume 71, Number 6

• Opinion against MR myelography
• States that lumbar puncture in patients with CSF leaks could be risky
• Cites no evidence
Case Series

First description of CSF to venous fistulas: 3 patients

Pros:
- describe new findings
- basis for more research

Cons:
- selection bias: doesn’t tell us much about patients with CVFs
- no comparator group

Digital subtraction myelography for the identification of spontaneous spinal CSF-venous fistulas

The “Hyperdense Paraspinal Vein” Sign: A Marker of CSF-Venous Fistula

Wouter I. Schievink, MD, Franklin G. Moser, MD, MMM, M. Marcel Maya, Ravi S. Prasad

Case Series

Epidural Blood Patch at C2: Diagnosis and Treatment of Spontaneous Intracranial Hypotension

- Single patient
- CSF leak at C2
- Successful treatment via targeted cervical patch
- Concludes targeted patching needed

False localizing sign of C1–2 cerebrospinal fluid leak in spontaneous intracranial hypotension

Wouter I. Schievink, M.D., M. Marcel Maya, M.D., and James Tourje, M.D.

- 25 patients
- 3 with C2 contrast
- All had surgically proven CSF leak elsewhere
- Contrast spills out at C1/2 → false localizing
A classification system of spontaneous spinal CSF leaks

- 568 patients
- Three types:
  - Type 1: dural tear (27%)
  - Type 2: diverticula (42%)
  - Type 3: CSF – venous fistula (2.5%)
  - Indeterminate (29%)
- Snapshot in time
  - prevalence of disease
  - describes characteristics of subtypes

- Limitations:
  - referral / selection bias
  - difficult to confirm causal relationships between predictors and SIH subtypes
- Study type does not answer questions about comparative efficacy of different treatments
Cohort Studies

- Several *retrospective* observational studies
- No *prospective* studies
- Strengths:
  - less costly and time-consuming than prospective and RCTs
  - allows for inference of causality
- Weaknesses:
  - limited control over quality and nature of data
    - may not have outcomes measured correctly or systematically
  - confounding
Cohort Studies

- Several retrospective observational studies
- No prospective studies

Strengths:
- Less costly and time-consuming than prospective studies
- Allows for inference of causality

Weaknesses:
- Limited control over quality and nature of data
- May not have outcomes measured correctly or systematically
- Confounding

Diagram:
- Type A
- Coffee -> MI
- Confounding
## Evidence for EBP in Treatment of SIH

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># Patients</th>
<th># BP</th>
<th>Targeted or Blind</th>
<th>Pro/Retro</th>
<th>Outcome metric</th>
<th>Follow up</th>
<th>Estimate of efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>He</td>
<td>2018</td>
<td>165</td>
<td>1-4</td>
<td>T</td>
<td>Retro</td>
<td>Subjective</td>
<td>1-7 years</td>
<td>88% with first patch, 7% second, 4% third, 0.6% fourth.</td>
</tr>
<tr>
<td>Wu</td>
<td>2017</td>
<td>150</td>
<td>1-3</td>
<td>T</td>
<td>Retro</td>
<td>Subjective</td>
<td>48 hr</td>
<td>59% with first patch, 33% second, 6% third. 2 pts (1.3%) not cured</td>
</tr>
<tr>
<td>Cho</td>
<td>2011</td>
<td>56</td>
<td>1</td>
<td>T+B</td>
<td>Retro</td>
<td>Subjective</td>
<td>6 mos-5.2 years</td>
<td>87% (targeted) vs 52% blind (p&lt;0.05)</td>
</tr>
<tr>
<td>Ferrante</td>
<td>2010</td>
<td>42</td>
<td>1-3</td>
<td>B</td>
<td>Retro</td>
<td>NS</td>
<td>1 mo, 3mos, 6mos-5yrs</td>
<td>90% with first, 5% second, 5% third</td>
</tr>
<tr>
<td>Chung</td>
<td>2005</td>
<td>53</td>
<td>1.5</td>
<td>(mean)</td>
<td>T+B</td>
<td>Subjective</td>
<td>1 mo</td>
<td>77% (targeted), 77% blind, 40% conservative</td>
</tr>
<tr>
<td>Berroir</td>
<td>2004</td>
<td>27</td>
<td>1-2</td>
<td>B</td>
<td>Retro</td>
<td>VAS decrease &gt;90%</td>
<td>1 month, 1-4 years</td>
<td>90% immediate relief, one third relapsed. Of relapses, 66% cured with second EBP. Total ‘cure’ 77%</td>
</tr>
<tr>
<td>Sencakova</td>
<td>2001</td>
<td>25</td>
<td>1-6</td>
<td>T+B</td>
<td>Retro</td>
<td>NS</td>
<td>NS</td>
<td>36% with 1st patch, 20% with second, then 6 went to surgery and 4 had 3-6 additional patches. Logistic regression showed trend toward improvement with targeting (p=0.07), OR not reported.</td>
</tr>
</tbody>
</table>

### EBP vs. Conservative

77% vs. 40% (p<0.05)
Randomized Controlled Trials

- Prospective, blinded, and randomized
- Randomization eliminates confounding
- Blinding reduces bias
- “Gold standard”
- SIH Literature: NONE
Vertebroplasty:
- place large needles into a vertebral body fracture
- inject “cement” to fix fracture

Industry sponsored case and unblinded nonrandomized studies suggested efficacy

Based on this → billion $ industry in USA

No prior RCTs
Randomized Controlled Trials

- 131 patients
- Randomized to vertebroplasty or simulated procedure
- Improvements in both groups
- No difference between the two groups!

A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures


Where are we going?
Cohort Studies

- Prospective observational studies
- Cedars-Sinai, Duke, Mayo
Unification via Registry

• Centralized registry:
  – GUIDs
  – Maximize:
    • geographic reach
    • data heterogeneity
    • data completeness

• Allows for epidemiology
RCTs: The PATCH Trial

- Sponsored by RSNA RSG
- Duke – single center
- Optimal treatment vs. Simulated procedure
- Prove patching works
The PATCH Trial

Primary Endpoint: HIT-6 at 1 month (reduction from baseline)

Inclusion Criteria:
- Adult
- Meets ICHD-3 SIH criteria
- MRI Brain with contrast
- Definite CSF leak on myelography
- Baseline HIT-6 > 56

Exclusion Criteria:
- Contraindication or inability to undergo procedure
- Recent blood patch (< 2 weeks)
- Inability to provide informed consent
- Expected inability to complete follow up
- Contraindication to contrast media or fibrin glue

Randomization

CT fluoroscopy-guided targeted blood and fibrin glue patch

CT fluoroscopy-guided targeted saline injection

1 week:
- Assess for Adverse Events

2 weeks:
- Outcome measures

1 month:
- Outcome measures

2 months:
- Patient Crossover Allowed

4 months:
- Outcome measures

Brain MRI: SIH findings
RCTs: Future Endeavors

• PATCH trial: multi-institutional
• Targeted vs. Non-targeted patching
• Blood vs. Fibrin glue
Conclusions

• Substantial progress over the past 10 – 15 years!

• But, we have a long way to go!

• Quality research needed – tough to do
  – Requires: dedication, organization
    leadership, funding

• The future is bright
Thank you!

Tim Amrhein, MD
Assistant Professor of Neuroradiology
Duke University Medical Center
@TimAmrheinMD