USING AN EVIDENCE-BASED APPROACH TO PDPH

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Goals & Objectives

• Describe the problem with using mechanistic theory and unsystematic observation for decision-making related to PDPH

• Use clinical scenarios and the evidence cycle to explore Prevention, Treatment, and Diagnosis of PDPH
Mechanistic Theories & Unsystematic Observations that Suggest *BEST* Practices Ultimately

- May be proven to be True
- May Also Be *Untrue*
  - Bloodletting
  - Ice gastric Lavage
  - Flecainide encainide for ventricular ectopy post acute MI
- Long term HRT Rx and Cardiovascular Protection
Classic Model of PDPH

- CSF leakage
- Traction on pain sensitive dural structures
  - “Traction headache” Ray (1940); Brownridge (1983); IHS 1988
  - “Low pressure headache IHS 2004”
- Referred pain
- Postural headache
- +auditory/visual sxs
Patient with spontaneous intracranial hypotension (SIH) before blood patch procedure. (D) Same patient after blood patch procedure and resolution of symptoms. Open arrows (C) denote abnormal venous sinus caliber before treatment; closed arrows (D) denote normalization of venous sinus caliber post-treatment.
Greene (1923) Dural Fibers Parallel & Longitudinal (Light Microscopy)

Dural Fibers: Light Microscopy x 20; (Angle, Kronberg, Thompson, Anesthesiology, 2003)
Are the Dural Fibers Really Parallel and Longitudinal?

Same Specimen of Grossly Normal Appearing Cadaveric Human Dura by Scanning and Transmission Electron Microscopy (Angle, Kronberg, Thompson, Anesthesiology, 2003)
Are Pencil Point Spinal Needles Really Atraumatic?

25g Whitacre Puncture. Arrow = collagen flaps at puncture borders (Reina, 2000)
Gormley Anesthesiology 1960
Do Bloody Spinal Taps Really Prevent Headache?

Clinical Evidence

**STRONG: Needle Gauge & Tip Design**

- **Systematic Reviews/Meta-analyses**
  - Halpern & Preston (1994)
  - Choi (2003)
- **Evidence-based Guideline (GemNet)**
- **Update American Academy of Neurologists (atraumatic needles) (J Neurology, 2005)**

**Weak:**

- **Needle bevel orientation**
  - Leighton and Norris, 1989
  - Ansaloni (Tropical Doctor, 2000)
  - Mihic 1985,
  - Flaaten 1998

**No Association between Bloody Taps as Prevention for PDPH**

- **Spinal needle literature**
  - Nelson (1930), Koster (1930)
  - Emory (19848), Harris (1953)

- **Epidural needle literature**
  - Khan (Anaesthesia 1993)
Cochrane SR: Blood Patch
(Boonmak & Boonmak, 2010)

• Role of Therapeutic and Prophylactic EBP for treating headache post DP is inconclusive.

• PEBP Not Recommended – too few trial participants to allow reliable conclusions to be drawn.

• While therapeutic EBP showed benefit over conservative Rx (based on limited evidence) reliable conclusions cannot be drawn re benefits and harms
Are Doctors Just Playing Hunches?

By CHRISTINE GORMAN  Thursday, Feb. 15, 2007

Sponsored Links

I Had High Blood Pressure
Now it's down to 120/75.
Find out how I did it
without drugs
www.resperate.com

Canadian Mom's
Tip: To
2. Evidence Based Clinical Practice

• “Involves integration of best research evidence, especially patient-centered research, with our clinical expertise and our patient’s unique circumstances and values.”

• Use of the “Evidence” alone in decision-making is never enough. There is always a trade off between benefits/risks, inconvenience, cost and patient’s values. (Straus 2005)

• Ultimate Importance of any intervention must be shown by it’s impact in Humans
Hierarchy of Evidence for Therapy

- Systematic Reviews/Meta-analyses of RCTs
- Single Large High Quality RCT
- Systematic Reviews of observational studies
- Physiologic studies (BP, Cardiac output etc)
- Unsystematic clinical observations (eg case reports, case series)

User’s Guide to the Medical Literature, JAMA, 2002
Critical Appraisal
Basic Design of A Randomized Controlled Trial

Intervention

Establishing the same baseline prognosis between groups

Maintaining prognostic balance

A

B

outcome

outcome

\[ \Delta \]
Estimation of Treatment Effect

Point Estimate (dot) & 95% Confidence Intervals

Benefits of Estimation vs Hypothesis testing (ie using p values)

1. Best estimate of the Degree of benefit
2. The degree to which we can have confidence in our findings
RANDOM ERROR & BIAS

**FIGURE 2B-1**

Representation of Four Sets of Identically Conducted Studies Demonstrating Varying Degrees of Bias and Random Error


User’s Guide to the Medical Literature, JAMA, 2008
Effect of Random Error via Stopping Rules
Five vs Four Courses of Therapy for Acute Myeloid Leukemia

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Deaths/Patients</th>
<th>Statistics (O-E)</th>
<th>Var.</th>
<th>HR &amp; 95% CI</th>
<th>Odds Redn. (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Five courses</td>
<td>Four courses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>7/102</td>
<td>15/100</td>
<td>-4.6</td>
<td>5.5</td>
<td>57% (29); 2P = 0.05</td>
</tr>
<tr>
<td>1998 (1)</td>
<td>23/171</td>
<td>42/169</td>
<td>-12.0</td>
<td>15.9</td>
<td>55% (10); 2P = 0.003</td>
</tr>
<tr>
<td>1998 (2)</td>
<td>41/240</td>
<td>66/240</td>
<td>-16.0</td>
<td>26.7</td>
<td>45% (15); 2P = 0.002</td>
</tr>
<tr>
<td>1999</td>
<td>51/312</td>
<td>69/309</td>
<td>-11.9</td>
<td>30.0</td>
<td>33% (15); 2P = 0.03</td>
</tr>
<tr>
<td>2000</td>
<td>79/349</td>
<td>91/345</td>
<td>-9.5</td>
<td>42.4</td>
<td>20% (14); 2P = 0.1</td>
</tr>
<tr>
<td>2001</td>
<td>106/431</td>
<td>113/432</td>
<td>-6.2</td>
<td>53.7</td>
<td>11% (13); 2P = 0.4</td>
</tr>
<tr>
<td>2002</td>
<td>157/537</td>
<td>140/541</td>
<td>6.7</td>
<td>74.0</td>
<td>-9% (12); 2P = 0.4</td>
</tr>
</tbody>
</table>

Wheatley K, Clayton D. Controlled Clinical Trials 2003;24:66-70
Slides From: Gordon Guyatt with permission
Evidence Cycle

1. ASSESS

2. ASK

PICOTT FORMAT

3. ACQUIRE

PubMED Clinical Queries & Tripdatabase.com

4. APPRAISE

Critical Appraisal sheets

5. APPLY

3. Clinical Scenarios
ASSESS: Clinical Scenario 1

• A 28yo OB/GYN resident has a recognized DP with a 17g Tuohy needle (LOR to NS) during early labor.
  – Are there any immediate interventions that might reduce her risk of PDPH?

• The epidural is placed successfully at another level and is functioning normally. She wants to know what if anything can be done to prevent PDPH
  – What will you tell her?
PDPH Prevention Following DP

ACUTE
• Stylet reinsertion ⭐
• Intrathecal saline
• Catheter insertion through the puncture site

SUBACUTE
• Prophylactic EBP
• Epidural Morphine
• ACTH/steroids
• Intrathecal/epidural saline
• Bedrest**
• Caffeine**
• Increased Fluid intake **
ASK: Searchable Question (PICOTT)

- **Population**: laboring obstetric patients with a recognized epidural needle puncture
- **Intervention**: reinsertion of the stylet
- **Comparator**: no reinsertion of the stylet
- **Outcome**: Incidence of PDPH
- **Type of Question**: Therapy
- **Type of Study Design**: high quality SR/Meta-analysis of high quality RCTs or High quality RCT
Search terms: headache and stylet

(See handout for steps and critical appraisal sheet for RCTS)

• 1. Google: PubMed clinical queries
  – To find Randomized trials:
    • Go to clinical study categories
    • Click on “therapy” and “narrow specific”
    • Enter: headache and stylet
  – To find systematic reviews (scroll down the page in clinical queries, use the same search terms.

• 2. Tripdatabase.com

3 articles all originating from a single RCT (Strupp, J Neurol 1998)
  Guideline for Rx of Alone Acute Severe Headache (GEMNet)
  Best Evidence Topic
  Letter to the Editor (Strupp, NEJM, 1997)
Does Restyletting the Epidural Needle prior to removal post ADP reduce PDPH? (Strupp 1998)

• Single Ctr well-conducted RCT
• **Population**: 600 neurology pts without headache undergoing Dx LP, 21g Sprotte needle
• **Intervention**: Stylet replaced prior to needle withdrawal (n=300)
• **Comparator**: stylet not replaced (n=300)
• **Outcome**: Incidence of PDPH≤ 7 days* (had to have some posturality for dx)
Strupp (Results)

PDPH Incidence:
- EXPTL group (stylet replaced): 15/300 = (5%)
- CTRL group (not replaced): 49/300 = (16%)

• Relative Risk (RR) = 5%/16% = 0.3
• Relative Risk Reduction (RRR) = 1 - 0.3 = 0.7 (95% CI, 0.47, 0.82)
• = 70% reduction in the risk of PDPH if the stylet is replaced

• Risk Difference (RD) = 16% - 5% = 11%
• Number Needed to Treat (NNT) = 100%/RD = 100%/11% = 9
• You have to restylet the needle prior to withdrawal in 9 patients to prevent PDPH in one additional patient undergoing Dx LP

• Secondary Outcomes: Less severe headache with stylet replaced (p<0.02)
• Harms/ Side effects: none noted
Other In vitro Evidence Supporting a Mechanism at the Dural level?

• Bela Hatfalvi
  • Noted failure of some DPs to leak post spinal needle puncture

• Angle (Anesthesiology, 2003)
  • Epidural needle work
  • Failure of some DPs to leak regardless of epidural needle type
  • Scanning EM showed dural fragments plugging the DP site
Evidence Cycle

1. **ASSESS**
   - Benefits?
   - S/E, Harms?
   - Costs? Pt preferences?

2. **ASK**
   - PICOTT FORMAT

3. **ACQUIRE**
   - PubMed Clinical Queries & Tripdatabase.com

4. **APPRAISE**
   - Critical Appraisal sheets

5. **APPLY**
Does Injection of Intrathecal Saline at the time of ADP decrease PDPH? (Charsley, RAPM, 2001)

- *Non randomized trial*
- Population: 54 pts with recognized ADP (most were obs pts).
- Intervention: 28 pts received IT saline 10ml (6 via spinal catheter)
- Comparator: 26 concurrent pts received no saline (5 received an IT catheter)
- Primary outcome: postural headache ≤ 2wks.
Results (Charsley, 2001)

- Overall Incidence of PDPH all pts:
  - Saline: 7/28 (25%) vs No Saline: 16/26 (62%) (p=0.01).
  - RRR =0.60 (95% 0.2,0.80)
  - Overall EBP: Fewer EBPs with Saline: 1/28 vs 10/26

- Incidence of PDPH Injection through the Needle
  - Saline: 7/22 (32%) vs No Saline: 13/28 (46%) p=0.07
    - RR 0.51 (0.26, 1.03)
  - EBP: Saline group 1/22 (5%) vs No saline: 9/28 (32%)
Do Intrathecal Catheters or Epidural Saline Boluses Prevent PDPH (Apfel, BJA. 2010)

- SR Meta-analysis
  - 17 studies of over 1200 pts, included Non RCTs
  - 12 studies – all non-RCTs, Epidural saline boluses or IT catheters
- Epidural Saline boluses  RR 0.65, (0.4, 1.05)
- Intrathecal Catheter placement (RR 0.21 (0.02, 2.61)
  - IT Catheter x 1 day: No preventive effect  RR 0.88 (0.68, 1.14)
  - IT Catheter longer than 24 hours. Mixed results but still not significant  RR 0.21 (.02, 2.65)
Bedrest, Fluid Intake, Caffeine

Prolonged Bed rest does not prevent PDPH
• SR Meta-analysis: Thoennissen, (CMAJ, 2001)
• 16 RCTs, (anesthesia, myelography, Dx LP)
• Immediate/short term vs long term bedrest more than 2000 pts
• No difference in PDPH
  RR 0.93 (0.81, 1.08) myelography
  RR 0.97 (0.79, 1.19) Dx group

Fluid Intake Does Not Prevent PDPH.
• RCT: Dieterich (Eur Arch Psychiatry Neurol Sci 1988).
  – 100 age matched neurology pts sp LP.
  Exptl: 1.5L per day fluid vs 3.0 L per day x 5 days. No difference in PDPH btwn groups.

Caffeine for Prevention & Rx of PDPH
• 3 trials (Yucel 1999, Esmaglou, 2005 Camann 1990 ) small size, methodologically flawed.
• No pharmacological basis or clinical trial evidence to support use of caffeine.
Does Prophylactic EBP Reduce PDPH after Recognized ADP?

- 2 SR/Meta-analyses (Apfel BJA 2010, Cochrane, 2010)

- Boonmak & Boonmak, Cochrane 2010
  - 6/9 RCTS related to PEBP, 265pts
  - Studies compared PEBP to no blood patch, epidural saline infusion, sham EBP
    - Primary Outcome: Postural headache improved with lying down.
    - Potential harms (infection, backache, lower limb paresthesia)
  - Only one high quality RCT (Scavone), showed no difference in PDPH incidence
Does Prophylactic EBP Reduce PDPH after Recognized ADP? (Scavone, 2004)

• Single Ctr. Well-conducted RCT.
• **Population:** 64 Obs pts with ADP (17g) during labor analgesia/anesthesia
• **Intervention:** PEBP (20ml)
• **Comparator:** Sham EBP (n=32 per arm) post delivery
• **Outcome:** Primary outcome, PDPH (standardized definition) ≤5days of DP
• Secondary outcomes: PDPH severity, duration, opioid use, backpain, use of therapeutic EBP (protocol-based, none used before 24hrs)
Scavone, Anesthesiology, 2004
Prophylactic EBP vs Sham EBP

- PEBP 18/32= 56%
- Sham 18/32=56%

- RR=56%PEBP ÷ 56%sham EBP =1
- 95% CI (0.65, 1.53)

- Benefit=up to a 35% RRR in PEBP group
- NNT =5

25% RRR =Threshold for Treatment

Favors Treatment

RR of PDPH

Benefit=up to a 35% RRR in PEBP group

NNT =5
Secondary Outcomes (Scavone)

- No Differences Between Groups in:
  - PDPH Onset, maximum PDPH Pain scores
  - Inability to perform childcare, use of TX EBP
- P-EBP Group:
  - Decreased duration (p< 0.05)
  - Decreased pain intensity x duration (p<0.05)
- Conclusions:
  - Suggests no difference in PDPH incidence (negative but inconclusive study).
  - PEBP may decrease severity/duration of PDPH
**Does Epidural Morphine Prevent PDPH after Recognized ADP?** (Metwalli, Anaesthesia, 2008)

- **Single Ctr RCT. Multiple issues with Quality of Reporting**
- **Population:** 50 Laboring women, ADP (17g needle)
- **Intervention:** Epidural morphine (2 doses of 3mg diluted to 10ml with NS, given post delivery and again 24hours later)
- **Comparator:** NS (10ml given post delivery via the epidural catheter and again 24hours later)
- **Outcome:** Implied: PDPH (STD definition, including postural neckache) < 5days post epidural placement
  - Secondary Outcomes: HA severity, EBP use, NV, pruritus, Urinary retention, Respiratory depression.
What are the Results?

**PDPH +:**
- Epimorph: $3/25=12\%$
- Nsaline: $12/25=48\%$

**RR of PDPH:** $12\%/48\% = 0.25 \text{ (95\%CI 0.08, 0.69)}$

**Relative Risk Reduction:**
$1-0.25 = 0.75$

**Risk Difference:**
$\%\text{CTRL} - \%\text{Epimorph groups} = 48\% - 12\% = 36\%$

**Number Needed to Treat:**
$100\%/36\% = 2.8 = 3$

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**Treatment Threshold:** 25% Relative Risk Reduction

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Favors Epimorph
---

Favors Saline
## How Robust are These Findings?

<table>
<thead>
<tr>
<th></th>
<th>PDPH Positive</th>
<th>PDPH Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epimorph +</strong></td>
<td><strong>5</strong> (previously 3)</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td><strong>Epimorph -</strong></td>
<td>12</td>
<td><strong>15</strong> (previously 13)</td>
<td>27</td>
</tr>
</tbody>
</table>

**P=0.077**

**Rule of Thumb:** if adding a handful of outcomes in the opposite direction changes study findings, apply study findings with caution.
What About Secondary Outcomes?
(Al-Metwalli)

Table 2  PDPH and treatment outcome.

<table>
<thead>
<tr>
<th></th>
<th>Morphine (n = 25)</th>
<th>Saline (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence of PDPH</td>
<td>3.0 (12%)</td>
<td>12.0 (48%)</td>
</tr>
<tr>
<td>Onset of PDPH; days</td>
<td>3.0 (3–4 [3, 4])</td>
<td>2.0 (1–2.5 [1–3])</td>
</tr>
<tr>
<td>Maximum VRSP; (0–10)</td>
<td>5.0 (4–5 [4–5])</td>
<td>6.0 (4–7 [3–8])</td>
</tr>
<tr>
<td>Recommended therapeutic EBP</td>
<td>0.0</td>
<td>6.0 (24%)</td>
</tr>
<tr>
<td>Therapeutic EBP performed</td>
<td>0.0</td>
<td>4.0 (16%)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>11.0 (44%)</td>
<td>4.0 (16%)</td>
</tr>
<tr>
<td>Itching</td>
<td>3.0 (12%)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

PDPH, post dural puncture headache; VRSP, verbal rating scale of pain; EBP, epidural blood patch.
Values are median (IQR [range]) or number (proportion).

What about Urinary retention? They say none occurred. Doesn't fit with the MacArthur paper.
Does Cosyntropin (ACTH Analogue) Prevent PDPH post ADP? (Hakim, Anesthesiology 2010)

- Single Ctr RCT
- **Population**: 95 parturients with recognized ADP, labor epidural (16-18g), LOR NS, vaginal delivery
- **Intervention**: Cosyntropin (1mg diluted in 4ml NS given iv over 5minutes) at 30min post delivery
- **Comparator**: Normal saline (4ml)
- **Outcome**: Incidence of PDPH, STD definition with Dx 5 days of ADP).
Hakim

- Exclusion criteria: PET/HTN, DM, fever, WBC
- Mgt: Admitted 48 hours, expectant mgt, EBP for persistent severe headache after 48hrs.
- Followup: Twice daily visits by a blinded assessor, followup phone call at 14 days. Additional 14 day f/up if EBP given
- Secondary outcomes: VAS scores for headache, EBP use
Methodologic Issues (Hakim)

• Single author study
• Unclear Allocation: ? Randomization table: accessible to anesthesiologists on L&D at the time of recruitment ?
• Other prognostic information not reported (eg headache history)
• All of the patients developed PDPH within 48 hours of ADP and all EBPs done within 48 hrs. (unusual)
• Other side-effects
What are the Results? (Hakim)

PDPH +
Cosyntrontin: 15/45=33%
Saline: 31/45 (69%)

RR PDPH = 33%/69%
= 0.48, 95% CI (0.32, 0.74)

Relative Risk Reduction =
1- 0.48 = 0.52

Risk Difference =
%CTRL - % Cosyntrontin group
= 69%-33% = 36%

Number Needed to Treat =
= 100%/36%=
= 2.8 =3
Worst Case Scenario (Hakim)

Add 2 to ACTH group with PDPH, 15 becomes 17

Lastly Apply the Rule of thumb: Add an additional 2 pts with PDPH to RX arm and 3 without PDPH to CTRL arm: results reach statistical significance (p=0.027. RR 0.63 (0.42, 0.93))
Hakim (2010)

• **Secondary Outcomes**
  
  • Cosyntropin group dvpt PDPH later (27 hours) vs 17hrs in NS group
  
  • **EBP:**
    – Cosyntropin: 5/45 (11%)
    – NS group: 13/45 (29%) \( p=0.035 \)
  
  • Similar headache severity and rates of Repeat EBP btwn groups
  
  • Side effects: urticarial rash 2 pts (Cosyntropin group)
Clinical Scenario 2

• You are called to see the same patient again for a moderate to severe postural neckache 24 hrs post epidural. She has mild dizziness and muffled hearing. She is otherwise well and had an uncomplicated vaginal birth.

• She wants to know if she has PDPH.

• What will you say?
Clinical Symptoms of PDPH

- **Classic Presentation (Brownridge, 1983)**
  - Postural bilateral headache, (posturality early on)
  - 50% frontal, 25% occipital, 25% neck pain
  - Auditory visual sx less than 1%

- **Retrospective Cohort (Angle, 1998)**
  - 25 cases of ADP
  - 80% (20/25) typical PDPH
  - 20% (5/25) atypical. 1 postural neckache only; 1 non postural neckache & auditory sx (both responded to Ebp)

- **Case reports: postural neck presentation**
  - Dunbar (CJA, 1995). 2 cases postural neck 1) or interscapular pain. (1) post steroid injection. Rx EBP
How Good are Diagnostic Criteria for PDPH After ADP (Angle, Preliminary Data, Canadian PDPH Collaborative)

- Multicenter RCT, blinding pt (attempted), assessor, treating physicians, adjudicators, statistician blinded.
  - Population: 1080 laboring pts
  - Intervention: large (18-16g) epidural needle
  - Comparator: small (19g) epidural needle
  - Outcome: PDPH (by study definition) 14 days of epidural.

- Longitudinal followup of all patients adjudicated positive for PDPH to sx resolution or one year.

- Adjudicators simultaneous rated pts for PDPH by study and IHS criteria.
# Diagnostic Criteria for PDPH Post Epidural

<table>
<thead>
<tr>
<th>Formal Study Criteria</th>
<th>IHS Criteria (ICHD-II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Postural HA or Neckache that occurs or worsens within 15 minutes of sitting/standing and improves within 15 minutes of lying down. Symptoms may include: visual or auditory symptoms; neck stiffness, tinnitus, diplopia, photophobia, nausea/vomiting.</td>
<td>1. Headache worsens within 15 minutes of sitting/standing and improves within 15 minutes of lying down with at least one of the following criteria (must include criteria 3 &amp; 4 as well); neck stiffness, tinnitus, photophobia, nausea, hypacusis.</td>
</tr>
<tr>
<td>2. Patients may or may not have a known or suspected dural puncture</td>
<td>2. Dural puncture has been performed</td>
</tr>
<tr>
<td>3. HA / Neckache persists at least 24 hours AND occurs within first 14 days of epidural placement</td>
<td>3. Headache develops within 5 days of dural puncture</td>
</tr>
<tr>
<td></td>
<td>4. Headache resolves within 1 week spontaneously OR within 48 hours of effective RX (ie EBP).</td>
</tr>
</tbody>
</table>
## Clinical Course by Adjudicators’ Final Dx

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>+ BOTH Criteria N=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recognized or Suspected DP (yes)</td>
<td>6/13</td>
</tr>
<tr>
<td>Onset postural Sx (median, IQR)</td>
<td>2 (1,3)</td>
</tr>
<tr>
<td>Severity ≤14days or pre EBP (VAS/10)</td>
<td>7.8 ± 1.2</td>
</tr>
<tr>
<td>Postural Neckache</td>
<td>4/13</td>
</tr>
<tr>
<td>Neck + Assoc Sx</td>
<td>2</td>
</tr>
<tr>
<td>Neck No Assoc Sxs</td>
<td>2 (DP, EBP, no childcare x 7days)</td>
</tr>
<tr>
<td>EBP =1 received</td>
<td>(4)</td>
</tr>
<tr>
<td>Duration</td>
<td>4 days ± 2 (excluding 1 dvpt chronic HA, NO EBP, sx to 1 year)</td>
</tr>
<tr>
<td># Women unable to perform childcare ≤14days</td>
<td>6/11</td>
</tr>
<tr>
<td>If unable to perform childcare, # days</td>
<td>4 ± 2.4 (1-7days)</td>
</tr>
</tbody>
</table>
## Clinical Course by Adjudicators’ Final Dx

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>+ Study Definition Only n=12</th>
<th>+ IHS Only n=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recognized or Suspected DP (yes)</td>
<td>0/12</td>
<td>1/3</td>
</tr>
<tr>
<td>Onset postural Sx (median, IQR)</td>
<td>Day 6 (3, 12)</td>
<td>Day 1 (3/3)</td>
</tr>
<tr>
<td>Worst Severity ≤ 14 days or pre EBP (VAS/10)</td>
<td>5.7 ± 2.6</td>
<td>6 ± 4.0</td>
</tr>
<tr>
<td></td>
<td>5. ± 2.3 (excluding EBP pt)</td>
<td></td>
</tr>
<tr>
<td>Postural Neckache only</td>
<td>5/12</td>
<td>1/3</td>
</tr>
<tr>
<td>EBP =1 received/rec</td>
<td>2 EBPs (1 patient)/0</td>
<td>0</td>
</tr>
<tr>
<td>Duration</td>
<td>8 women: 5.5 (3,8)</td>
<td>2-5 hours</td>
</tr>
<tr>
<td></td>
<td>&gt;6wks : 4/12;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(&gt;13wks : 2/12</td>
<td></td>
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<tr>
<td></td>
<td>≥6mos: 1/12 (Failed EBP x2))</td>
<td></td>
</tr>
<tr>
<td># women unable to perform childcare ≤ 14days</td>
<td>1/12 (60 days, Failed EBP x2)</td>
<td>0</td>
</tr>
</tbody>
</table>
Performance of Formal Study vs IHS Criteria

• Interrater reliability (first pass agreement)

• Formal Study Criteria:
  – 0.93 (95% CI 0.85, 1.0)
    • very good

• IHS Criteria:
  – kappa 0.70 (95% CI 0.49, 0.92)
Clinical Scenario 3

• At 48 hours the patient now has a postural headache and neckache with the same associated sxs. She wants to know if an EBP will cure her.

• What will you say?
How Effective is Epidural Blood Patch for Treatment of PDPH after ADP (van Kooten, 2008)

• Single ctr RCT: assessor blinded. 2Pts in CTRL arm withdrew post randomization.

• Population: Neurology Pts (42) sp Dx LP.
  – All had mod-severe pdph lasting > 24 to 7 days
  – Dx by neurologist

• Intervention: Therapeutic EBP (15-20ml)

• Comparator: fluid best rest x 7 days

• Outcome: any headache at 24hrs post EBP
Treatment effect: Primary Outcome

At 24 hours Headache was present in:

<table>
<thead>
<tr>
<th></th>
<th>PDPH</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>11</td>
<td>No</td>
</tr>
<tr>
<td>EBP</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>NO EBP</td>
<td>19</td>
<td>2</td>
</tr>
</tbody>
</table>

- RRR = 1 - 0.64 = 0.36 (a 36% reduction in the risk of PDPH at 24 hours)
- NNT = 100%/Risk Difference = 100%/32% = 3

EBP group 10/11 were mild vs 19/19 were mod to severe
Differences in recovery rates over time: p < 0.0001 log rank
At 7 days: fewer cases of Headache in EBP group and these were less severe
If outcomes are split 1:1
Worst Case Scenario

JAVA STAT http://statpages.org/ctab2x2.html
Summary

- Described the problems with relying on mechanistic theory and unsystematic observation for clinical decision-making
- Illustrated concepts related to use of the evidence cycle
- Applied to important or emerging concepts related to PDPH
PDPH Trial Collaborators

- **Steering Committee:** P Angle (Primary Investigator), J Kronberg, S Halpern
- **Safety and Data Monitoring Committee:** J Kronberg (Chair), A Kiss (Statistician), P Morely-Forster
- **Study Adjudicators:** M Gawel (Neurologist), P Morely-Forster, J Kronberg, J Douglas
- **Trial Coordinating Center:** Obstetric Anesthesia Research Unit (OARU), Sunnybrook Research Institute, University of Toronto.
- **Biostatistical Unit:** Dept Research Design & Biostats, Sunnybrook HSC, Toronto: A Kiss, M Katic
- **Trial Coordinators:** J Yee, Lisa O’Brien, Research Assistants: M Haley, J Djordjevic, S Goril, S Ahmed
- **Study Sites:**
  - Sunnybrook HSC Trial Site: P Angle, A Banerjee, R Stocche, M Davallou
  - IWK Hospital: R George, D McKeen, F Jacobson, D Wells, K Wallace
  - BC Women’s Hospital: J Douglas, R Preston,
  - St Joseph’s Health Center, University of Western Ontario: I Singh, S. Dhir, M. Silva
Start Search Strategy for Epidural morphine prophylaxis PICOTT
PubMed is a service of the National Library of Medicine, providing access to over 12 million MEDLINE citations back to the mid-1960s and additional life science journals. PubMed includes links to many sites providing full-text articles and other related resources.

**Bookshelf Additions**

The KTR Gene Cluster, written by Mary Carrington and Paul Norman, is now available for interactive searching on the Bookshelf.

**New PubMed Features**

The Summary page displays a new icon link for free full-text articles.

New data and additional search options, including an e-mail selection, have been added to PubMed. See New/Noteworthy.
PubMed Clinical Queries

This page provides the following specialized PubMed searches for clinicians:

- Search by Clinical Study Category
- Find Systematic Reviews
- Medical Genetics Searches

After running one of these searches, you may further refine your results using PubMed's *Limit* feature.

Results of searches on these pages are limited to specific clinical research areas. For comprehensive searches, use PubMed directly.

### Search by Clinical Study Category

This search finds citations that correspond to a specific clinical study category. The search may be either broad and sensitive or narrow and specific. The search filters are based on the work of Haynes RR et al. See the filter table for details.

**Search** epidural morphine and headache  
**Go**

<table>
<thead>
<tr>
<th>Category</th>
<th>Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>etiology</td>
<td>narrow, specific search</td>
</tr>
<tr>
<td>diagnosis</td>
<td>broad, sensitive search</td>
</tr>
<tr>
<td>therapy</td>
<td></td>
</tr>
<tr>
<td>prognosis</td>
<td></td>
</tr>
</tbody>
</table>
Search by Clinical Study Category

This search finds citations that correspond to a specific clinical study category. The search may be either broad and sensitive or narrow and specific. The search filters are based on the work of Haynes RB et al. See the filter table for details.

Search [epidural morphine and headache] Go

<table>
<thead>
<tr>
<th>Category</th>
<th>Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>etiology</td>
<td>narrow, specific search</td>
</tr>
<tr>
<td>diagnosis</td>
<td>broad, sensitive search</td>
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<tr>
<td>therapy</td>
<td></td>
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<tr>
<td>prognosis</td>
<td></td>
</tr>
<tr>
<td>clinical prediction guides</td>
<td></td>
</tr>
</tbody>
</table>

Find Systematic Reviews

For your topic(s) of interest, this search finds citations for systematic reviews, meta-analyses, reviews of clinical trials, evidence-based medicine, consensus development conferences, and guidelines.

For more information, see Help. See also related sources for systematic review searching.

Search [ ] Go

Medical Genetics Searches

This search finds citations and abstracts related to various topics in medical genetics. See the filter table for details.
(epidural morphine and headache) AND (randomized controlled trial) Publication:

1. Epidural morphine injections for prevention of postaural puncture headache.

2. The use of intrathecal morphine for postoperative pain relief after liver resection: a comparison with epidural analgesia.

3. Maternal satisfaction to epidural and spinal anesthesia for cesarean section.

4. Comparison of technical and block characteristics of different combined spinal and epidural anesthesia techniques.
   - Puolakka R, Pitkänen MT, Rosenberg PH.
Search Trip Database for "epidural morphine and headache"

Below are links to articles providing background knowledge relating to headache:

- CKS Guideline
- eMedicine Background
- eMedicine Diagnosis
- eMedicine Treatment
- eMedicine Follow-up
- Mentor
- GP Notebook
- Wikipedia
- Wrong Diagnosis
- Search Trip just for "headache"

Order By: Data Relevance

Filter Your Search

Total: 29

- Evidence Based Synopses: 0
1. Epidural morphine injections for prevention of post dural puncture headache.
   - Anaesthesia 2008

2. Ultrasound-guided catheterisation of the epidural space
   - National Institute for Health and Clinical Excellence - Interventional Procedures 2008

3. The use of intrathecal morphine for postoperative pain relief after liver resection: a comparison with epidural analgesia
Critical Appraisal

• Are the Results Valid?
  • Did treatment and control groups start with the same prognosis?
  • Was this balance maintained as the study progressed?
  • At the completion of the study?

• What are the Results?
  • How Large is the treatment effect?
  • How Precise is the Rx effect?

• Can I apply them in my care?
  • Were the pts studied similar to my patients?
  • Were all clinically important outcomes considered?
  • Are the treatment benefits worth the potential harms (risks, side-effects) and costs?

User’s Guide to the Medical Literature, JAMA, 2002
S. Förderreuther Neurology 2001;57:527-529. Dilated Cervical Veins 1. T2-weighted MRI (sagittal plane) showing the dilated anterior venous plexus (arrows) with a significant flow void (increased flow) in a patient with severe orthostatic headache. This was found in 8/8 patients with severe OH. Extraarachnoid fluid collections were also found in 7/8 patients.
### A

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Intervention</th>
<th>Control</th>
<th>Risk ratio</th>
<th>Risk ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td><strong>1.1.1 Epidural saline vs no saline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craft and colleagues&lt;sup&gt;25&lt;/sup&gt;</td>
<td>2</td>
<td>16</td>
<td>13</td>
<td>17</td>
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<tr>
<td>Brownridge&lt;sup&gt;18&lt;/sup&gt;</td>
<td>24</td>
<td>37</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Trivedi and colleagues&lt;sup&gt;24&lt;/sup&gt;</td>
<td>20</td>
<td>30</td>
<td>21</td>
<td>24</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
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<td><strong>60</strong></td>
<td><strong>21.0%</strong></td>
<td><strong>60</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>46</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2=0.11$; $\chi^2=7.12$, df=2 ($P=0.03$); $I^2=72%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**1.1.2 Intrathecal saline vs no intrathecal saline**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Control</th>
<th>Risk ratio</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Charsley&lt;sup&gt;26&lt;/sup&gt;</td>
<td>7</td>
<td>22</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>22</strong></td>
<td><strong>21</strong></td>
<td><strong>5.8%</strong></td>
<td><strong>21</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>7</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**1.1.3 Short-term intrathecal catheter vs no catheter**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Control</th>
<th>Risk ratio</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Cohen and colleagues&lt;sup&gt;28&lt;/sup&gt;</td>
<td>8</td>
<td>17</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Norris and Leighton&lt;sup&gt;29&lt;/sup&gt;</td>
<td>19</td>
<td>35</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Ayad and colleagues&lt;sup&gt;27&lt;/sup&gt;</td>
<td>18</td>
<td>35</td>
<td>34</td>
<td>37</td>
</tr>
<tr>
<td>Rutter and colleagues&lt;sup&gt;31&lt;/sup&gt;</td>
<td>24</td>
<td>34</td>
<td>30</td>
<td>37</td>
</tr>
<tr>
<td>Paech and colleagues&lt;sup&gt;30&lt;/sup&gt;</td>
<td>21</td>
<td>24</td>
<td>44</td>
<td>51</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>145</strong></td>
<td><strong>161</strong></td>
<td><strong>40.2%</strong></td>
<td><strong>161</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>90</td>
<td>124</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2=0.05$; $\chi^2=11.02$, df=4 ($P=0.03$); $I^2=64%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**1.1.4 Long-term intrathecal catheter vs no intrathecal catheter**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Control</th>
<th>Risk ratio</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Cohen and colleagues&lt;sup&gt;28&lt;/sup&gt;</td>
<td>0</td>
<td>13</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Ayad and colleagues&lt;sup&gt;27&lt;/sup&gt;</td>
<td>2</td>
<td>31</td>
<td>34</td>
<td>37</td>
</tr>
<tr>
<td>Kaul and colleagues&lt;sup&gt;20&lt;/sup&gt;</td>
<td>30</td>
<td>60</td>
<td>84</td>
<td>162</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>104</strong></td>
<td><strong>214</strong></td>
<td><strong>12.5%</strong></td>
<td><strong>214</strong></td>
</tr>
<tr>
<td>Total events</td>
<td>32</td>
<td>123</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2=4.23$; $\chi^2=23.07$, df=2 ($P=0.00001$); $I^2=91%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PEBP: Boonmak Cochrane SR 2010

• Ackerman 21 Obs pts with ADP (18-20ml blood)
• Colonna 39 Obs pts with ADP (15ml blood)
• Lowenwirt: 49 Obs pts (15-20ml)

• Sengupta 48 spinal anesthesia pts (18-60yrs)
• 10ml blood.
• Scavone 64 Obs pts with ADP (18-20ml)
• All RCTs but 1 (Scavone, Anesthesiology 2004) suggested a benefit of PEBP
• All were of poor methodologic quality except 1 (Scavone)

<table>
<thead>
<tr>
<th>Outcome: PDPH</th>
<th>Peto Odds Ratio, Fixed Effects Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDPH:</td>
<td>PEBP vs Conservative RX</td>
</tr>
<tr>
<td>Ackerman</td>
<td>Ackerman 1/10 7/11 OR 0.11(0.02,0.64)</td>
</tr>
<tr>
<td>Colonna</td>
<td>Colonna 4/19 16/20 OR 0.1(0.03 0.35)</td>
</tr>
<tr>
<td>Lowenwirt</td>
<td>Lowenwirt 4/24 24/25 OR 0.04 (0.01,0.03) OR 0.06 (0.03,0.14)</td>
</tr>
<tr>
<td>PDPH:</td>
<td>PEBP vs Epidural Saline</td>
</tr>
<tr>
<td>Sengupta</td>
<td>Sengupta 2/24 11/24 OR 0.16(0.04, 0.55)</td>
</tr>
<tr>
<td>PEBP vs Sham</td>
<td>Scavone 18/32 18/32 OR 1 (0.38, 2.66)</td>
</tr>
</tbody>
</table>

Favors PEBP OR=1 Favors CTRL