Comparison of Morphine, Hydromorphone and Fentanyl for Post-operative Pain Control in Patients Undergoing Open Bowel Surgery

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Objectives

- Background
  - Laparotomy
  - Neuraxial opioids

- Research Proposal
  - Review of the literature
  - Objectives and hypotheses
  - Proposed Methodology

- Issues

- Questions & Feedback
Laparotomy

- Exploratory vs. Therapeutic
- Midline (T8-12)
- Subcostal or Chevron (T6-12)
Background

- Epidural infusions can be used for post operative analgesia
- Typical infusions combine a local anesthetic with opioid
- Many choices for epidural opioids
  - morphine, fentanyl, hydromorphone, sufentanil, pethidine (meperidine)
  - which is best?
Pharmacology

- Absorption:
  - Regional: into epidural fat, white and gray matter of cord, cerebrum via CSF
  - Systemic: vascular uptake

- Opioids can be categorized as hydrophilic vs. lipophilic
  - Fentanyl (lipophilic)
  - Morphine (hydrophilic)
  - Hydromorphone (intermediate)
Pharmacology

- **Hydrophilic:**
  - Slower onset/elimination
  - Widespread CSF distribution (better coverage but potential resp. depress)
  - Increased risk of pruritis, sedation
  - Better gray matter penetration (enhanced potency)

- **Lipophilic**
  - More rapid onset/shorter duration
  - Narrow segment distribution
  - Rapid systemic absorption
Side Effects of Opioids:

For all Opioids:

- Nausea: 25%
- Vomiting: 20%
- Pruritis: 16%
- Sedation: 14%, excessive sedation 3%
- Visual disturbance 6-7%
Question

- Which opioid is ideal?
  - Effective
  - Few side effects

- Given hydromorphone’s intermediate level of lipophilicity, it may be as effective as morphine but with a side effect profile like fentanyl

- What does the literature suggest?
Literature review

- Metanalysis to assess for optimal opioid (underway)
- Computerized search of EMBASE, Medline, CCTR for English language studies
- 18 RCTs retrieved for epidural post-op analgesia for abdominal surgery. No SR.
<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Opioid Comparison</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al (2006)</td>
<td>RCT</td>
<td>Sufentanil vs. Morphine</td>
<td>Urine output (S&lt;M)</td>
<td>Pruritis, N/V (S&lt;M)</td>
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<tr>
<td>Gastrectomy with thoracic</td>
<td>N=60</td>
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<tr>
<td>epidural (TE)</td>
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<td>Valairucha et al (2005)</td>
<td>RCT</td>
<td>Fentanyl vs. Morphine</td>
<td>Pruritis (F=M)</td>
<td>N/V (F&lt;M)</td>
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<tr>
<td>Thoracotomy/Upper</td>
<td>N=90</td>
<td></td>
<td></td>
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<tr>
<td>abdominal surgery (TE)</td>
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<tr>
<td>Ozalp et al (1998)</td>
<td>RCT</td>
<td>Fentanyl vs. Morphine</td>
<td>Did not specify: Pain/Sedation (F=M)</td>
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<tr>
<td>Major abdominal surgery</td>
<td>N=40</td>
<td></td>
<td>Nausea/Pruritis (F&lt;M)</td>
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<td>(LE)</td>
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<td>Motor weakness (1 pt in F vs. 0 in M)</td>
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<tr>
<td>Smith et al (1996)</td>
<td>RCT</td>
<td>Fentanyl vs. Diamorphine vs. Pethidine</td>
<td>Did not specify: Pain (F=D=P)</td>
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<tr>
<td>Laparotomy** (TE)</td>
<td>N=60</td>
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<td>Pruritis (P&lt;D, F)</td>
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<td>Motor block (D&gt;P,F)</td>
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<tr>
<td>Cox et al (1996)</td>
<td>RCT</td>
<td>Fentanyl vs. Pethidine</td>
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<td>Major abdominal surgery</td>
<td>N=40</td>
<td></td>
<td>Pruritis/Sedation/Motor Block (F=P)</td>
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<td>Pulmonary function tests (F=P)</td>
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<td>Saito et al (1994)</td>
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<td>Thoracic or abdominal</td>
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<td>Hypotension, pruritis (F&lt;M)</td>
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<td>No respiratory depression in either</td>
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<td>Comparison</td>
<td>Primary</td>
<td>Secondary</td>
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<td>Wilhelm (1993) Thoracotomy/Aorta/Bowel Surgery</td>
<td>RCT N=53</td>
<td>Fentanyl vs. Sufentanil</td>
<td>Did not specify: Pain (F=S) BP, HR, Sedation/Nausea/Pruritis (F=S)</td>
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Research Proposal

- Few studies assessing hydromorphone
- 1 study comparing to morphine:
  - Similar analgesia, greater pruritis with M
  - Combined thoracic/abdominal/pelvic surgery
- 1 study comparing to morphine/fentanyl:
  - Pediatric orthopedic surgery
- A lack of literature exists in this area
Objectives

1. “To compare the effectiveness of morphine, fentanyl and hydromorphone when administered by epidural infusion for post-operative analgesia, among patients who have undergone a laparotomy”

2. “As a secondary objective, we wish to also compare the side effect profiles of these epidural opioids”
Hypothesis

1. Hydromorphone provides non-inferior pain control compared to morphine and fentanyl

2. Hydromorphone will have a more favorable side-effect profile (including PONV, pruritus and sedation)
Methodology

- RCT
- "Double-blind"
  - Patients, outcome adjudicators, physicians and nursing
  - Research pharmacist will be aware of group allocation

- PICOT
  - population, intervention/comparison, outcome, timing
Population

■ Inclusion criteria:
  - all laparotomy patients who require epidural analgesia for postoperative pain control
  - E.g. bowel, liver or whipple surgery
  - Setting: Juravinski Hospital in 2011

■ Exclusion criteria:
  - Gynecologic surgery
  - Contraindications to study drugs or neuraxial anesthesia
  - Patients taking opioids for chronic pain (except T3 and percocet) and other long acting opioids
  - Lack of consent by the patient or surgery team for inclusion
Intervention/Comparison

Three treatment arms:

A. 0.05 mg/mL Morphine + 0.125% bupivicaine
B. 2 mcg/mL Fentanyl + 0.125% bupivicaine
C. 20 mcg/mL Hydromorphone + 0.125% bupivicaine
Outcomes

1. Change in Visual Analogue Pain Score (VAS)
   - At rest, measured on POD#2

2. Frequency of:
   - PONV
   - Pruritis
   - Sedation
   - Respiratory depression
   - Motor block

3. Other measures: pain on POD#0,1,2 at rest and while coughing, hypoxia, hypotension, hallucinations
Anesthetic Management

- Intra-operative opioids will be limited to remifentanil and sufentanil
- Epidural:
  - T8-12 (midline/paramedian) or T6-T12 if included subcostal and chevron incisions
  - Test dose/bolus: 3 cc of 0.25% bupivacaine with 1:200,000 epinephrine
  - Infusion/bolus with study drug (4-10 cc/hr)
Statistical Analysis

- Non-inferiority study
- Alpha: 0.05
- Beta: 0.80
- Statistical comparisons will be made using ANOVA testing
- Sample size to be determined
Potential Issues:

- **Epidural failure**
  - IV analgesia or epidural restart if pain > 8/10 for 2 hours
  - Intention to treat, exclude in subgroup analysis

- **Potential confounders:**
  - Surgical type and duration
  - Incision type
  - Weight?
  - Others?
Questions and Feedback