Current Issues in Postoperative Pain Management

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Barts and The London NHS Trust
Outline

• Types of acute pain
  – issues and unmet clinical needs

• Mechanisms

• Evidence underpinning current strategies

• Current clinical issues
  – Safety and risk assessment in analgesic treatments
    • Neuraxial blocks; PCA
  – Emerging techniques
    • new routes / formulations of established analgesics
    • new entities

  – Emerging issues
Acute Pain

• Trauma
• Medical
• Surgical
Clinical characteristics of Acute Pain

- Sudden, sharp, intense, localised
- Usually self-limited
- Consequences
  - Neuro-endocrine, Cardio-Respiratory, Gastrointestinal, Urinary
  - Musculoskeletal

Acute pain meta-analysis -165 papers
20,000 patients

Major surgery

Incidence of moderately severe to severe pain

IM / PCA / Epidural analgesia

<table>
<thead>
<tr>
<th></th>
<th>Severe pain %</th>
<th>Hypoventilation % (95% CI)</th>
<th>Hypotension % Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM analgesia</td>
<td>29.1</td>
<td>0.8 (0.2-2.5)</td>
<td>3.8 (1.9-7.5)</td>
</tr>
<tr>
<td>PCA</td>
<td>10.4</td>
<td>1.2 (0.7-1.9)</td>
<td>0.4 (0.1-1.9)</td>
</tr>
<tr>
<td>Epidural analgesia</td>
<td>7.8</td>
<td>1.1 (0.6-1.9)</td>
<td>5.6 (3.0-10.2)</td>
</tr>
</tbody>
</table>

Dolin SJ, Cashman JN, Bland JM. BJA. 2002; 89(3);409-423
Inadequate post-operative pain control *Analgesia Gaps*

Pain – post-operative recommendations

- APS
- Multimodal therapy
- Treat early
- Non-opioids
  ‘By the Clock’

- Salicylates
- Acetaminophen
- Opioids

Inhibit prostaglandin synthesis

NSAIDs
Improving Strategies

• Resources / Logistics / Systemic strategies
• Evidence based improvements in practice / Education:
  – Meta-analysis; NNT / NNH
  – Guidelines
  – Procedure specific recommendations (PROSPECT)
  – Pain 5th Vital Sign
  – RADAR: Responsibility, Anticipation, Discussion, Assessment, Response
  – Pain-OUT EU study:
    • Benchmarking across 11 European centres
    • Knowledge Library

Multimodal Analgesia

- Reduced doses of each analgesic
- Improved pain relief
- Synergistic / additive effects
- Reduces severity of side effects of each drug

Multimodal Therapy: Diclofenac ± Paracetamol ± Codeine

D = 100 mg diclofenac alone;
P = 1 g paracetamol alone;
P+C = 1 g paracetamol plus 60 mg codeine;
D+P = single oral dose 100-mg enteric-coated diclofenac with 1 g paracetamol;
D+P+C = 100-mg enteric-coated diclofenac with 1 g paracetamol plus 60 mg codeine

Opioid Related Side Effects

Warfield CA, Kahn CH. Anesthesiology 1995;83:1090-1094. (Survey of 500 U.S. adults)

Frequency of side effects (% of patients)

- Drowsiness: 32%
- Nausea: 32%
- Constipation: 9%
- Dizziness: 5%

Warfield CA, Kahn CH. Anesthesiology 1995;83:1090-1094. (Survey of 500 U.S. adults)
### Symptom Distress Questionnaire

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Did not have</th>
<th>(If yes), how often did you have it?</th>
<th>(If yes), how severe was it usually?</th>
<th>(If yes), how much did it distress or bother you?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rarely</td>
<td>Occasionally</td>
<td>Frequently</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inability to concentrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty with urination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retching/vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dose-related opioid-associated symptoms

‘Once threshold is reached, every further 3–4 mg increase will be associated with 1 clinically meaningful opioid-related symptom’

Zhao et al. J Pain Symptom Manage 2004;28:35
Multimodal therapy

Opioid sparing

• Much of our decision making is to avoid side effects and toxicity
Adjuvant analgesics for opioid sparing strategies

• Established
  – NSAIDs and coxibs (safety and tolerability issues)
  – Paracetamol
  – Local anaesthetic techniques

• Recent additional choices …….?
Adjuvant analgesics for opioid sparing strategies

- Established
  - NSAIDs and coxibs (safety and tolerability issues)
  - Paracetamol
  - Local anaesthetic techniques
- Recent additional choices
  - Gabapentin
  - Low dose ketamine
  - Dexamethasone
  - Duloxetine (BJA 2010)

Gabapentin in Post-operative Pain: Meta-analysis of 12 RCTs


Weighted mean difference (WMD) 95% CI

Pain at rest (20-24 hours) (n=355)

Pain at rest (0-4 hours) (n=424)

Analgesic (PCA opioid) consumption (n=372)

Ketamine Review

- Single IV ketamine bolus improved posto analgesia with opioids
  - side effects: not increased by a single bolus IV ketamine
- Minor surgical procedures, single dose ketamine ranging from 0.15–1 mg/kg in addition to opioids may be useful
- Despite opioid-sparing effects
  - no reduction in opioid-related side effects such as PONV, pruritus, and respiratory depression
- Small dose ketamine not associated with increased psychomimetic effects eg. hallucinations or excessive sedation
- To be researched:
  - Small dose ketamine used for acute postoperative pain to reduce long-term pain syndromes (postmastectomy, thoracotomy, and phantom pain)

Ketamine as Adjuvant Analgesic to Opioids: A Quantitative and Qualitative Systematic Review. K Subramaniam, B Subramaniam, R A Steinbrook Anesth Analg 2004;99:482–95
‘Recent’ Advances

• Only a few new entities
  • *in fact, we’ve lost more than we’ve gained*

• Most advances have been innovative ways to administer existing drugs:
  • local anaesthetic techniques
  • buccal
  • nasal
  • inhaled
  • controlled release
  • transdermal
    – passive & active
Postoperative Patient-controlled and Continuous Infusion Epidural Analgesia vs IV Opioid PCA
• Meta-analysis of 299 RCT’s
• Epidural analgesia in every combination superior to IV PCA up to 3-days (exception – epidural morphine alone)

RCT = Randomised controlled trial; PCA = Patient-controlled analgesia; IV = intravenous; PCEA = Patient controlled epidural analgesia; PONV = Post-operative nausea/vomiting.

Wu et al. Anesthesiology 2005;103:1079-88
Epidural Continuous Infusion Analgesia vs IV Opioid PCA

- Meta-analysis of 299 RCT’s
- Epidural analgesia in every combination superior to IV PCA up to 3-days (exception – epidural morphine alone)

- however, emerging safety data.............

RCT = Randomised controlled trial; PCA = Patient-controlled analgesia; IV = intravenous; PCEA = Patient controlled epidural analgesia; PONV = Post-operative nausea/vomiting.

Wu et al. *Anesthesiology* 2005;103:1079-88
Severe Neurological Complications after Central Neuraxial Blockades in Sweden 1990–1999

• Total approx. 1,260,000 spinals, 450,000 epidurals
• Severe neurological complications = 127; Permanent neurological damage = 85
  • Overall rate of: 1 in 8261
• Incidence after spinal = 1 in 25,000
  Obstetric epidural = 1 in 25,000
  Non-obstetric epidurals = 1 in 3,600
• Osteoporosis – previously neglected risk factor; common in women (↑ hip fractures, vertebral deformities, narrow spinal canal)

Moen et al. Anesthesiology 2004;101:950-9
Major complications of central neuraxial blocks:
3rd National Audit Project of Royal College of Anaesthetists (NAP3)

- 700,000 central neuraxial blocks over one year:
  - spinals 46%
  - epidurals 41%
  - (45% obstetric indications / 44% perioperative)

- 84 major complications:
  - 52 met all audit inclusion criteria
    - ‘pessimistic’ data interpretation:
      - 1 in 24,000 incidence of permanent injury
    - ‘optimistically’:
      - 1 in 54,000 incidence of permanent injury
Major complications of central neuraxial blocks:
3rd National Audit Project of Royal College of Anaesthetists (NAP3)

• **Deaths or paraplegias:**
  - ‘Pessimistically’ 13 cases 1 in 50,000
  - ‘Optimistically’ 5 cases 1 in 140,000

• **In the 30 patients with permanent harm:**
  - More than 80% of these patients had a CNB placed for perioperative analgesia
  - 60% occurred after epidural block
  - 23% after spinal anaesthesia
Epidural Analgesia

Benefits
- Superior analgesia
- Early ambulation
- Reduced morbidity
- Shorter hospitalization?

Costs
- Invasive technique
- Adverse effects
- Monitoring costs
- Neurol. complications
Sustained release epidural morphine

- 72 hours,
- ‘Single shot’

- No indwelling catheter
- No motor or sympathetic blockade

How to manage side effects when drug delivery cannot be stopped? (respiratory depression)
Sustained release epidural morphine

(EREM: Extended Release Epidural Morphine)

Viscusi et al. Anesthesiology. 2005;102
Electron Micrograph of a DepoFoam Particle

Bupivicaine for surgical wound infiltration

Positive Phase 2 studies 72 hours +

Morphine (epidural)
Inadequate post-operative pain control Analgesia Gaps

<table>
<thead>
<tr>
<th>Pain Level</th>
<th>1999</th>
<th>1993</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Pain</td>
<td>83</td>
<td>77</td>
</tr>
<tr>
<td>Slight Pain</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Moderate Pain</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>Severe Pain</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Extreme Pain</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
</table>

IV PCA - more analgesia gaps

Data pooled from the Hartrick and Minkowitz studies.

* P<0.001 vs. IV PCA Morphine

Panchal S. et al Poster presentation. ASRA 2006
Hartrick CT et al. Regional Anesthesia and Pain Medicine Vol. 31 No. 6 Nov-Dec 2006
Minkowitz HS et al. accepted to Pain Medicine. 2006
IV PCA - more analgesia gaps

“Press the button when you feel pain”

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IV PCA - more analgesia gaps

“Press the button when you feel pain”
- First you have to feel pain
…… always playing ‘catch-up’,
  • even worse after sleep
  • and only in small increments

Data pooled from the Hartrick and Minkowitz studies.
* P<0.001 vs. IV PCA Morphine

Panchal S. et al Poster presentation. ASRA 2006
Hartrick CT et al. Regional Anesthesia and Pain Medicine Vol. 31 No. 6 Nov-Dec 2006
Minkowitz HS et al. accepted to Pain Medicine. 2006
IV PCA: safety issues
Nearly 50% (63/131) of possible operator errors were associated with adverse events

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient death</td>
<td>6</td>
</tr>
<tr>
<td>Naloxone administered</td>
<td>41</td>
</tr>
<tr>
<td>Respiratory arrest</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>3</td>
</tr>
<tr>
<td>Oversedation</td>
<td>6</td>
</tr>
<tr>
<td>Unspecified</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>63</strong></td>
</tr>
</tbody>
</table>

Improved opioid strategies?

• Background, low rate infusions for PCA
• For patients able to take oral medicines
  – oral sustained release opioid plus immediate release
    • established practice in Germany

…. and with opioids, tolerability issues equally important
  – opioid sparing strategies
Iontophoretic Transdermal Delivery

- Iontophoresis: generally imperceptible electrical field transports 40mcg fentanyl dose through intact skin and into the bloodstream.

Zimmer R, Ashburn MA. Comp Ther 2001;27:293–301
Tapentadol
MOR agonism and NRI in pain models

Ascending pathway to the brain

Descending pathway from the brain

α₂-R

NA

Tapentadol

MOR

SP

Glu

pain signal
Bunionectomy: Efficacy
SPID-48 Hours (Primary Endpoint)

Higher SPID = greater pain relief

p<0.001 for all comparisons vs placebo

Dose dependent efficacy of Tapentadol

Daniels et al., CMRO 2009
Pooled Analysis of GI Adverse Events
Tapentadol IR Phase II/III Trials vs. Morphine

Data on file
Emerging issues in Acute Pain
Chronic Pain as an Outcome of Surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Perkins &amp; Kehlet %</th>
<th>Macrae %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy</td>
<td>11-49</td>
<td>23-49</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>22-67</td>
<td>5-67</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>3-56</td>
<td>3-27</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>0-37</td>
<td>15-63</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>-</td>
<td>0-37</td>
</tr>
</tbody>
</table>

Perioperative Oral Pregabalin Reduces Chronic Pain After Total Knee Arthroplasty

- Prospective RCT double-blind trial of pregabalin (300 mg) administered before TKA and for 14 days after TKA (150–50 mg twice daily)

- Neuropathic pain screen at 3 and 6 months post surgery
  - Leeds Assessment of Neuropathic Symptoms and Signs scale
  - Secondary outcomes
    - including knee range of motion, opioid consumption, postoperative pain scores, sleep disturbance, and

Perioperative Oral Pregabalin Reduces Chronic Pain After Total Knee Arthroplasty

Other outcomes: less opioid consumption, greater active flexion at 30 days

Perioperative Oral Pregabalin Reduces Chronic Pain After Total Knee Arthroplasty

• 240 patients randomised:
  – data for the primary outcome were obtained from 113 pregabalin patients and 115 placebo patients

At both 3 and 6 months post surgery:

• neuropathic pain was less frequent in the pregabalin group at 3 and 6 months
  – 0% vs. 8.7% and 5.2%, respectively in placebo group (P = 0.001 and P = 0.014).

• Pregabalin patients:
  – consumed less epidural and oral opioids (P = 0.003; P = 0.005)

Perioperative Oral Pregabalin Reduces Chronic Pain After Total Knee Arthroplasty

• Time to achieve hospital discharge criteria was longer for placebo patients, $69.0 \pm 16.0$ h (mean ± sd) vs. $60.2 \pm 15.8$ h ($P = 0.001$)
  – although no difference in actual duration of hospital stay

• Sedation ($P = 0.005$) and confusion ($P = 0.013$) were more frequent on the day of surgery and postoperative day 1 in patients receiving pregabalin

Opioid induced immunosuppression
Effects of morphine on immune cells in animals and humans

<table>
<thead>
<tr>
<th>Cell types</th>
<th>In vivo studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-lymphocytes</td>
<td>↓</td>
</tr>
<tr>
<td>B-lymphocytes</td>
<td>↓</td>
</tr>
<tr>
<td>Natural killer lymphocytes</td>
<td>↓</td>
</tr>
<tr>
<td>Monocytes/macrophages</td>
<td>↓</td>
</tr>
</tbody>
</table>

Not all opioids share the same immunosuppressive properties.

<table>
<thead>
<tr>
<th>Immunosuppressive</th>
<th>Less immunosuppressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Buprenorphine</td>
</tr>
<tr>
<td>Methadone</td>
<td>Hydromorphone</td>
</tr>
<tr>
<td>Morphine</td>
<td>Oxycodone</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Tramadol</td>
</tr>
<tr>
<td>Fentanyl</td>
<td></td>
</tr>
</tbody>
</table>
Anesthetic Technique for Radical Prostatectomy Surgery Affects Cancer Recurrence: A Retrospective Survey

- GA + Epidural or Morphine PCA
- Open prostatectomy surgery with general anesthesia, substituting epidural analgesia for postoperative opioids, was associated with substantially less risk of biochemical cancer recurrence.
- Prospective randomized trials to evaluate this association seem warranted

Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis?

*P = 0.038 comparing groups on Kaplan-Meier estimates at 24 months (z-test)
†P = 0.007 comparing groups on Kaplan-Meier estimates at 36 months (z-test)
Messages

- **Steady improvement, but pain levels still unacceptable:**
  - need analgesic measures working before patient awakens
  - strategy for when LA wears off
  - More continuous methods of pain relief (reduce analgesia gaps)

- **APS ‘In-patient’ Pain Service**
  - Medical and paediatric wards, chronic pain, etc
  - more integration with chronic pain service (*personal view*)
  - maintain education of ward staff:
    - To improve pain assessment and treatment
    - To maintain vigilance for potentially harmful complications
  - need to address training of new ‘acute pain’ consultants