RECENT ADVANCES IN ANALGESIA
Conflict of interests

- Paid honoraria lecturing and book chapters
- Editor of *Continuing Education in Anaesthesia, Critical Care & Pain*
- Assessor for MBBRACE-UK
- Committee member and website editor World ERAS® Society
- No shares in medical companies
Analgesia

Good analgesia cornerstone of modern perioperative care. It may allow:

• Earlier mobilization
• Reduced organ dysfunction
• Reduced stress response
• Earlier nutrition
• Earlier discharge home

Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms, resulting in additive or synergistic analgesia with lowered adverse effects of sole administration of individual analgesics.

Multimodal or balanced analgesia

Reduce opioid consumption by using:

- Local anaesthetics
- Systemic analgesics
Local anaesthetics
Local anesthetics

Central

- Neuroaxial blockade (epidural and spinal)
- Paravertebral
- Nerve/plexus blocks
- TAP block
- Rectus sheath catheters

Peripheral

- Wound catheters/infiltration
Local anesthetics

Central

Peripheral

Less popular

More popular
Why is central neuraxial block less popular?

**Epidurals**
- Not necessary (for small incision surgery)
- Failure rate
- Fluid management and hypotension
- Mobility
- Risks
- Length of stay increased
- BUT good for open/prolonged surgery

**Spinalis**
- Work well
- Fluid management and hypotension
- Risks
The non-working epidural

- Failure rate of epidurals up to 50% described

- Multifactorial
  - Technical
  - Pharmacological

- Active management
  - Adjuvants especially opioids
  - PCEA with background infusion
Transforaminal epidural catheter
Hypotension and fluids

- Hypotension and its effects on
  - Splanchnic and anastomotic perfusion
  - Other organs eg heart, brain, kidneys

- Treatment of hypotension
  - Fluids
  - Vasopressors
  - Pressure more important than flow

Gould TH. BJA 2002:89;446-51
Randomized clinical trial of epidural, spinal or patient-controlled analgesia for patients undergoing laparoscopic colorectal surgery

B. F. Levy¹, M. J. Scott², W. Fawcett², C. Fry³ and T. A. Rockall¹

¹Minimal Access Therapy Training Unit, ²Department of Anaesthesia and Intensive Care, Royal Surrey County Hospital, and ³Postgraduate Medical School, University of Surrey, Guildford, UK

Correspondence to: Mr B. F. Levy, Minimal Access Therapy Training Unit (MATTU), Daphne Jackson Road, Guildford GU2 7WG, UK
(e-mail: brucelevy22@hotmail.com)
Fluids and weight gain

- More patients required further iv fluids after 24 hours in epidural group

<table>
<thead>
<tr>
<th></th>
<th>Spinal</th>
<th>Epidural</th>
<th>PCA</th>
<th>Kruskal-Wallis</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Patients</td>
<td>6.4%</td>
<td>22.6%</td>
<td>3.3%</td>
<td>p=0.028</td>
</tr>
</tbody>
</table>

- Weight gain (kg):

<table>
<thead>
<tr>
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<th>Epidural</th>
<th>PCA</th>
<th>Kruskal-Wallis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) maximum weight gain</td>
<td>1.8 (0.8-2.8)</td>
<td>2.73 (1.60-4.45)</td>
<td>1.6 (1.03-3.00)</td>
<td>p=0.029</td>
</tr>
</tbody>
</table>
Mobilization – support for standing day one

<table>
<thead>
<tr>
<th></th>
<th>Spinal</th>
<th>Epidural</th>
<th>PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No help required</td>
<td>71%</td>
<td>20%</td>
<td>73%</td>
</tr>
<tr>
<td>One person required</td>
<td>29%</td>
<td>33%</td>
<td>27%</td>
</tr>
<tr>
<td>Two people required</td>
<td>0</td>
<td>44%</td>
<td>0</td>
</tr>
<tr>
<td>Not safe with two people</td>
<td>0</td>
<td>3%</td>
<td>0</td>
</tr>
</tbody>
</table>
Risks of epidurals

Neurological damage – NAP 3

- Permanent injury 1:24 000 to 1:54 000
- Death/paraplegia 1:50 000 to 1:140 000
- 2.5 x more likely epidurals cf spinals

http://www.rcoa.ac.uk/nap3
Where to nurse epidural patients

Need location that has:

- Adequate patient throughput
- Main ward
- Regular observations
- Able to treat:
  - breakthrough pain
  - hypotension
• We used spinals successfully for first 23-hour stay laparoscopic colectomy paper.
Spinals

- Well tolerated
- Early pain scores similar to epidurals; both better than PCA
- Good opioid sparing effect
- Less postoperative fluids and weight gain than epidurals
- Quicker return of bowel function than both epidural and PCA
- Urinary catheter removed more quickly
- Improved mobilisation
- Reduced length of stay
- Not suitable for prolonged or open surgery

Levy BF et al. BJS 2011;98:1068-1078
## Length of stay (days)

<table>
<thead>
<tr>
<th></th>
<th>Spinal</th>
<th>Epidural</th>
<th>PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>2.7</td>
<td>3.7*</td>
<td>2.75</td>
</tr>
</tbody>
</table>

*Levy BF et al. BJS 2011;98:1068-1078*
Rectus sheath blocks

• Limited good quality data
• Used especially for gynaecological and urological surgery
• Also herniae (children)
• Catheters can be inserted under direct vision, loss of resistance or by ultrasound
• LA via pump or bolus dosing
Rectus sheath blocks

• Better than wound catheters (qv)
• Opioid sparing
• Avoids mobility/hypotension associated with epidural
• Training of staff
• RCT underway comparing Thoracic Epidural versus Rectus Sheath Catheters (TERSC)
• Early data suggests can be comparable to epidural

Wilkinson KA et al. Trials 2014;15:400
TAP blocks

- Transversus abdominus plane block
- Many use ultrasound guidance
- Convincing opioid sparing effect for both open surgery (75%) and laparoscopic surgery (50%)
- Better evidence base than Rectus Sheath catheters
- Used in general surgical, gynaecological, obstetrics and urology
- Subcostal TAP block now used for upper abdominal surgery

El-Dawlatly AA et al. BJA 2009;102:763-7
TAP blocks - ultrasound

Needle tip can be hard to visualise – infiltrate 2-4mls of saline to ensure correct placement
TAP blocks

- TAP > iv paracetamol/oral analgesia > PCA
- Resumption of diet 12, 12, 36 hours respectively (P<0.001)
- Median LOS 2, 3, 5 days respectively (P<0.001)
  
  Zafar N, Colorectal Disease 2010;12:119-124

- Meta analyses supports its use in both open surgery and laparoscopic colorectal surgery for systemic analgesia
  
  Johns N et al. Colorectal Disease 201214: e635–e642

- However analgesic quality for TAP blocks generally inferior to central blocks for colorectal, LSCS and gastrectomy
Surgical Site Catheter Analgesia

Practical issues

• Catheter type
  – multiholed
• Catheter placement for abdominal surgery
  – preperitoneal > subcutaneous
• Bolus or Infusion. Flow rates
  – infusion > bolus.
  – high rates eg 10 mls/hr
• Duration
  – 48 hours
• For use at home?
Surgical Site Catheter Analgesia

• Varying results:
  – Opioid scores invariably reduced
  – Overall pain scores generally down
  – Some have shown reduced length of stay
  – Some have shown accelerated return of bowel function
  – Infection not increased

Karthikesalingham A et al. World J Gastroenterol. 2008; 14: 5301-5305
Beaussier M et al. Anesthesiology 2007; 07: 461-8
Surgical Site Catheter Analgesia

- LSCS: better analgesia, less side effects, less need for nursing care, shorter duration of stay compared with epidural morphine
  

- Open colorectal surgery: Comparable pain scores (slightly worse on movement) but less for urinary retention.
  

- Orthopaedics: Also of benefit in following knee > hip surgery
  
Peripheral ‘novel’ LA

- Local anaesthetic techniques demonstrated a significant reduction in opiate requirement at 48 hours. Local anaesthetic techniques were also associated with lower pain scores on movement at 24 and 48 hours, shorter length of stay, and earlier resumption of diet.

Ventham NT Dis Colon Rectum 2014;57:237-50
Systemic analgesics
Problems with systemic analgesics

- Opioids
- NSAIDs
- Paracetamol
- Local anaesthetics
- Steroids
- Clonidine
- Ketamine
- Magnesium
Problems with systemic analgesics

- Opioids: 
  - sedation, dysphoria, constipation, PONV
- NSAIDs: 
  - renal, bleeding, perforation, healing, CVS risk
- Paracetamol: hepatotoxicity
- Local anaesthetics: cardiac and CNS toxicity
- Steroids: hyperglycaemia, poor wound healing
- Clonidine: sedation, hypotension
- Ketamine: dysphoria
- Magnesium: hypotension, weakness
Healing and anti-inflammatory drugs

- Delayed bone union in some orthopedic models (< smoking!)
- Increased risk of anastomotic leakage with diclofenac treatment after laparoscopic colorectal surgery
- Cyclo-oxygenase 2 inhibitors and the risk of anastomotic leakage after fast track colonic surgery

  Holte K et al. BJS 2009;96:650-4

- Unresolved after five years – hopefully answered soon?

Lidocaine infusions

- Reduction in analgesic requirements, ileus and PONV
- Opioid consumption reduced by 2/3
- Reduced hospital stay

BUT

- May be less relevant in small incision vs classical open surgery

Marrett E et al BJS 2008;95:1331-1338

Lidocaine infusions

• Similar impact on bowel function to thoracic epidural
  Wongyingsinn, M et al. Regional anesthesia and pain medicine 2011;36:241-248

• Intraoperative infusion (only) also decreased opioid consumption and hospital LOS after gastrectomy

• Established and recommended as second line therapy
  Joshi GP et al. Colorectal Disease 2013;15:146-155
Ketamine

- Enjoying a resurgence 50 years after it was first synthesized
- N-methyl-D-aspartate (NMDA) glutamate receptor antagonist
- Synergistic/additive effect to morphine
- May prevent opioid-induced hyperalgesia (OIH) and chronic pain syndromes
- Dose and duration debated
Ketamine

When used intraoperatively and via infusion for 48 hours post op (2 mcg/kg/min after a 0.5 mg/kg bolus):

- Morphine consumption halved
- Side effects: sedation, delusions, nightmares, psychiatric disorders not manifest at these doses

Ketamine – 2 good reviews

Ketamine both reduces opioid consumption and improves analgesic quality:
• Less PONV, sedation but more nightmares/hallucinations
• Good for thoracic, upper GI and major orthopaedics
• Administered at different times
  – preemptively, intraoperatively, postoperatively
• and by different methods
  – bolus, infusion, PCA

Laskowski K et al. Can J Anaesth 2011;58:911-23

Adding ketamine to morphine PCA
• Mixed drugs were superior to PCA opioid alone in thoracic surgery with significant reduction in
  – pain score
  – total morphine consumption
  – postoperative desaturation.

Carstensen M et al. BJA 2010;104:401-406
Gabapentinoids

Pregabalin and gabapentin:
- Reduce postoperative pain
- Good opioid sparing effect
- Reduced opioid side effects
- Dose, duration unknown
- BUT: Pregabalin produces visual disturbances

Zhang J et al BJA 2011;106:454-462

- Not used for colorectal surgery but used successfully for laparoscopic cholecystectomy

Agarwal A et al BJA 2008;101: 700-704

- Recent review suggests they prevent chronic post surgical pain.

Procedure Specific Postoperative Pain Management

- Colonic Resection
- Radical Prostatectomy
- Breast (non cosmetic)
- Haemorrhoids
- Abdominal Hysterectomy
- Total Hip Arthroplasty
- Total Knee Arthroplasty
- Thoracotomy
- Hernia
- Laparoscopic Cholecystectomy

http://www.postoppain.org/
The Future
Analgesic effect on cancer outcome

- Regional anesthesia potentially improves outcome for some specialties (breast and prostate)
- ER patients may be fitter for adjuvant treatment more quickly (eg chemotherapy)
- Sympathetic block may improve cellular immunity
- Drug effects
  - Morphine and effects on NK cells
  - lignocaine demethylates DNA cancer cells
ANALGESIC EFFECT ON CANCER OUTCOME

**Effect of anaesthetic technique and other perioperative factors on cancer recurrence**

G. L. Snyder¹,²* and S. Greenberg¹,²

¹ Department of Anesthesia and Perioperative Medicine and ² Department of Oncology and Hematology, University of California, San Francisco, 505 Parnassus Ave., San Francisco, CA 94143, USA

**Cancer biology, analgesics, and anaesthetics: is there a link?**

L. A. Colvin¹*, M. T. Fallon² and D. J. Buggy³,⁴

¹ Department of Anaesthesia, Critical Care and Pain Medicine, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK
² Edinburgh Cancer Research Centre, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK
³ Department of Anaesthesia, The Mater Misericordiae Hospital, Dublin 7, Ireland
⁴ Outcomes Research Consortium, Cleveland Clinic, OH, USA
Analgesic effect on cancer outcome

- Not so far in Colorectal in retrospective analysis

- Nor gynaecological (ovarian or cervical)
Analgesic effect on cancer outcome

- 503 patients long-term follow up from prospective RCT in which patients were randomly assigned to receive general anaesthesia with or without epidural block for at least 3 postoperative days.

- “Use of epidural block in abdominal surgery for cancer is not associated with improved cancer-free survival”

Myles PS et al. BMJ 2011;342:d1491
• Can anaesthetic technique improve long term survival?
Summary

• Analgesia is key component of ERAS pathways
• Constantly challenge dogma
• Mainstay is multimodal analgesia
  – Regular oral analgesia (paracetamol/NSAIDs)
  – Opioid sparing
  – LA (peripheral) where feasible
• As surgery changes so does analgesia
  – Open ≠ Laparoscopic
  – Epidurals have a declining place
• Active management of problems
  – PONV
  – Weakness
  – Hypotension
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