Epidural Analgesia: The Best Mix

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Conflicts of Interest
Introduction

• Childbirth is painful
• Neuraxial analgesia is the most efficacious option available to expectant mothers
• In Australia/New Zealand
  • Over 50% of mothers will have epidural analgesia
  • Over 100,000 epidurals performed per annum
• Despite epidural popularity and numbers, best practice evidence is limited
• Significant equipoise exists
Why is this topic important?

- Obstetric anaesthesia is a consumer focused specialty
  - Mothers expect the highest quality care to be provided
  - Epidural analgesia is controversial
- Epidural analgesia may have a significant impact on
  - Maternal motor blockade
  - Maternal hypotension
  - Duration of labour
  - Mode of delivery
  - Neonatal outcomes
  - Maternal fever
  - Staff workload
Scope of Talk

• Brief revision of labour pain
• What is the best epidural “mix”
  • Delivery method
  • Pharmacology
    • Local anaesthetic
    • Opioid
  • PCEA options
    • Bolus volume
    • Lockout interval
    • Background administration techniques
  • Other additives for consideration
• Not in scope: initiation or breakthrough analgesia options

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Labour pain: A brief revision

• Some unique features:
  • A progressive increase in intensity
    • Increased dose, decreased duration of action of LA’s
  • Dynamic
    • A change in innervation as labour progresses
  • Influenced by multiple maternal and fetal factors
    • Nulliparous versus multiparous
    • Fetal position
    • Spontaneous versus induced labour

Analgesia provided must be flexible enough to meet the changing demands as labour progresses
What is the best epidural mix?
What is the best epidural mix?

• Lets put the KEMH protocol under scrutiny:
  • PCEA: CADD Solis pump
    • Local anaesthetic: 0.0625% bupivacaine
    • Opioid additive: 2.5 µg /ml fentanyl
    • Other additives: Clonidine (rare)
  • Bolus volume: 10 ml
  • Lockout interval: 20 mins
  • Background technique: 5 ml continuous infusion
What is the best drug delivery technique?

Bolus techniques are better than continuous infusions

- PCEA first described in 1988
  - Now considered best practice
- Associated with:
  - Increased maternal satisfaction
  - Improved second stage analgesia
  - Decreased local anaesthetic consumption
  - Decreased clinician interventions
  - Decreased motor blockade

Kaynar: Anesth Analg 1999

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Which local anaesthetic?

“The analgesic efficacy depends mainly on the concentration rather than the type of anaesthetic used”

Which concentration of local?

Low concentration solutions are associated with improved maternal outcomes

• High concentration solutions are generally not required in labour
• Low concentration solutions:
  • Allow higher volumes to be administered, enhancing epidural spread
    • Eg: ED$_{50}$ bupivacaine 0.125% is 25% lower than 0.25%
  • Provide analgesia with less sympathetic changes
• What is a “low” concentration?

Aim: <0.1% bupivacaine and <0.17% ropivacaine
How strong is the evidence?

Level One evidence shows significant benefits of low concentration solutions

- Low concentration solutions
  - Decreased assisted delivery (OR 0.7)
  - Shorter second stage (14 minutes)
  - Less urinary retention (OR 0.42)
  - Less LA consumption
  - Less motor block, greater ambulation
  - No change in caesarean delivery

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Should we add an opioid?

• Fentanyl and sufentanil most widely studied
• Minimal evidence to guide the most appropriate concentration with modern PCEA approaches
• Opioids associated with
  • Improved analgesia
  • Decreased local anaesthetic
  • Decreased motor block
  • Decreased hypotension
• But: increased side effects: pruritus/nausea
PCEA: bolus volume and lockout interval

- Large number of study designs
  - 2-20 ml bolus doses
  - 5-30 min lockout intervals

“no strong evidence to favour one regimen over another”

“there is a suggestion that high volume/long lockout intervals provide better labour analgesia”

Halpern and Carvalho: Anesth and Analg 2009
PCEA: bolus volume and lockout interval

- Large number of study designs
- 2-20 ml bolus doses
- 5-30 min lockout intervals

0.4 ml
4 ml
10 ml

Hogan, Anesthesiology 1999
Whether a continuous infusion should be utilized is controversial

- ASA 2017 Practice Guidelines provide no clear guidance
- High rate (≥5ml/hr) infusions appear more efficacious
- Documented benefits include decreased breakthrough pain, lower physician interventions
- But: higher overall LA consumption, potentially more motor block
Continuous infusions: The good

Heeson et al, Anesth Analg 2016

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCEA + CI</th>
<th>PCEA</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Missant, 2005</td>
<td>10</td>
<td>40</td>
<td>0.35 [0.20, 0.62]</td>
<td>0.35 [0.25, 0.47]</td>
</tr>
<tr>
<td>Lim, 2008</td>
<td>28</td>
<td>200</td>
<td>0.33 [0.22, 0.49]</td>
<td></td>
</tr>
<tr>
<td>Brogly, 2011</td>
<td>2</td>
<td>20</td>
<td>0.57 [0.31, 0.96]</td>
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<tr>
<td>Haydon, 2011</td>
<td>5</td>
<td>87</td>
<td>0.40 [0.15, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>347</td>
<td>239</td>
<td>0.35 [0.25, 0.47]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>45</td>
<td>85</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00, Chi² = 8.5, df = 3 (P = 0.23), I² = 0%
Test for overall effect: Z = 6.01 (P < 0.00001)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCEA+CI</th>
<th>PCEA</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SD</td>
<td>Total</td>
<td>IV, Random, 95% CI</td>
<td>Year</td>
</tr>
<tr>
<td>Vallejo, 2007</td>
<td>7.75</td>
<td>3.5</td>
<td>-0.75 [-2.06, -0.56]</td>
<td>2007</td>
</tr>
<tr>
<td>Haydon, 2011</td>
<td>2.9</td>
<td>4.5</td>
<td>-1.90 [-3.11, -0.69]</td>
<td>2011</td>
</tr>
<tr>
<td>Brogly, 2011</td>
<td>1.25</td>
<td>0.5</td>
<td>-4.00 [-6.48, -1.64]</td>
<td>2011</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>171</td>
<td>164</td>
<td>-2.27 [-4.26, -0.27]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 2.77, Chi² = 19.45, df = 2 (P = 0.0001); I² = 90%
Test for overall effect: Z = 2.23 (P = 0.03)
Continuous infusions: The bad

⇧ Local anaesthetic consumption

⇧ Instrumental deliveries

⇧ Duration of second stage
Mandatory bolus techniques
Mandatory bolus techniques

Programmed Bolus

PCEA Bolus

Programmed Bolus

Programmed Bolus

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Automated intermittent epidural boluses improve analgesia induced by intrathecal fentanyl during labour

[L’administration automatisée de bolus intermittents améliore l’analgésie induite par du fentanyl intrathécal pendant le travail]

Sebastian M.H. Chua MMED,* Alex T.H. Sia MMED†

Purpose: We compared the efficacy of epidural continual intermittent bolus (CIB) with a continuous epidural infusion (CEI) in prolonging labour analgesia induced by the combined spinal epidural (CSE) technique.

Methods: CSE was instituted in 42 nulliparous parturients at the L3 to L4 level with intrathecal (IT) fentanyl 25 μg followed by an epidural test dose of 3 mL of 1.5% lidocaine. These parturients were then randomly assigned to receive either epidural CIB (n = 21) or CEI (n = 21) with 0.1% ropivacaine and fentanyl 2 μg mL⁻¹. For the CIB, 5 mL boluses were given hourly, with the first bolus 30 min postinduction. CEI at the rate of 5 mL h⁻¹ was initiated in the minute after CSE. The duration of analgesia, pain score, degree of sensorimotor block were compared.

Results: From Kaplan Meier survival analysis, the duration of analgesia was significantly longer in CIB (mean survival time 239 ± SD 24 min vs 181 ± 17, P < 0.05 using log rank test). During the first three hours postblock, the median sensory block to cold was higher in CIB (48.8 ± 11.6 cm) than CEI (32.6 ± 11.6 cm) and the difference was significant (P < 0.05).

Objective: Compare the efficacy of bolus péridurales intermittents administrées en continu (CIB) avec la perfusion péridurale continue (CEI) comme analgésie prolongée pendant le travail induite selon une technique rachidienne péridurale combinée (RPC).

Méthode: L’analgésie RPC a été installée chez 42 parturientes nullipares au niveau L3 à 4 avec 25 μg de fentanyl intrathécal (IT) suivi d’une dose test péridurale de 3 mL de lidocaïne à 1,5 %. Les patientes ont été randomisées pour recevoir soit des CIB périduraux (n = 21), soit une CEI (n = 21) avec ropivacaine 0,1 % et 2 μg mL⁻¹ de fentanyl. Dans le cas des CIB, des bolus de 5 mL à chaque heure ont été donnés, dans le premier 30 min après l’induction. La RPC a débuté une minute après la RPC à raison de 5 mL h⁻¹. La durée de l’analgésie, les scores de douleur et le degré de bloc sensorimoteur ont été comparés.

Résultats: A partir de l’analyse de survie de Kaplan Meier, on a trouvé une analgésie significativement plus longue avec les CIB (temps de survie moyen de 239 ± l’erreur type 24 min vs 181 ± 17, P < 0.05). Au cours des trois premières heures postblock, le bloc sensoriel à la température d’eau était plus élevé dans le CIB (48.8 ± 11.6 cm) que dans la CEI (32.6 ± 11.6 cm) et la différence était significative (P < 0.05).
Programmed/mandatory bolus techniques

continuous infusion

bolus injection

JUST DO IT.
Intermittent Epidural Bolus Compared with Continuous Epidural Infusions for Labor Analgesia: A Systematic Review and Meta-Analysis

Ronald B. George, MD, FRCPC, * Terrence K. Allen, MBBS, FRCA, † and Ashraf S. Habib, MB, ChB, MSc, MHS, FRCA ‡

Anesthesia & Analgesia 2013
## Table 2. Summary of Randomized Controlled Trials Meta-analysis Findings Comparing PIEB and CEI or PCEA With a Background Infusion for Labor Analgesia

<table>
<thead>
<tr>
<th></th>
<th>PIEB Versus CEI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local anesthetic consumption (MD)</td>
<td>−1.2 mg/h (95% CI, −2.2 to −0.3)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Maternal satisfaction scores (MD)</td>
<td>7.0 mm (95% CI, 6.20 to 7.8)</td>
<td>&lt;0.00001*</td>
</tr>
<tr>
<td>Duration of second stage of labor (MD)</td>
<td>−12 min (95% CI, −23 to 0)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean delivery (OR)</td>
<td>0.87 (95% CI, 0.56 to 1.35)</td>
<td>0.54</td>
</tr>
<tr>
<td>Instrumented delivery (OR)</td>
<td>0.59 (95% CI, 0.35 to 1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Total duration of labor (MD)</td>
<td>−12 min (95% CI, −23 to 0)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Anesthesia interventions (OR)</td>
<td>0.56 (95% CI, 0.29 to 1.06)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Local anesthetic consumption presented as milligram of bupivacaine equivalents per hour; Satisfaction measured using 0–100 mm scale.

Abbreviations: CEI, continuous epidural infusion; CI, confidence interval; MD, mean difference; OR, odds ratio; PCEA, patient-controlled epidural analgesia; PIEB, programmed intermittent epidural bolus.

*aFavors PIEB over CEI.
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Parity</th>
<th>Combined spinal epidural–subarachnoid medications</th>
<th>Epidural solution</th>
<th>CEI regimen</th>
<th>IEB regimen</th>
<th>Spontaneous/induced labor, n (%)</th>
<th>Risk of bias assessment</th>
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</thead>
<tbody>
<tr>
<td>Capogna et al.</td>
<td>145</td>
<td>Nulliparous</td>
<td>N/A</td>
<td>Levobupivacaine, 0.0625%–0.125%; sufentanil, 0.5 µg/mL</td>
<td>10 mL/h (0.0625%) + PCEA (5 mL bolus, 10 minute lockout, 0.125%) (n = 70)</td>
<td>10 mL (0.0625%) bolus every hour + PCEA (5 mL bolus, 10 minute lockout, 0.125%) (n = 75)</td>
<td>Spontaneous labora; oxytocin use not reported</td>
<td>Low risk</td>
</tr>
<tr>
<td>Chua and Sia</td>
<td>42</td>
<td>Nulliparous</td>
<td>Fentanyl, 25 µg</td>
<td>Ropivacaine, 0.1%; fentanyl, 2 µg/mL</td>
<td>5 mL/h (n = 21)</td>
<td>5 mL bolus every hour (n = 21)</td>
<td></td>
<td>Low risk</td>
</tr>
<tr>
<td>Fettes et al.</td>
<td>40</td>
<td>Nulliparous</td>
<td>N/A</td>
<td>Ropivacaine, 0.2%; fentanyl, 2 µg/mL</td>
<td>10 mL/h (n = 20)</td>
<td>10 mL bolus every hour (n = 20)</td>
<td></td>
<td>Low risk</td>
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<tr>
<td>Leo et al.</td>
<td>62</td>
<td>Nulliparous</td>
<td>Ropivacaine, 2 mg; fentanyl, 15 µg</td>
<td>Ropivacaine 0.1%; fentanyl 2 µg/mL</td>
<td>5 mL/h + PCEA (5 mL bolus, 10 minute lockout) (n = 31)</td>
<td>5 mL bolus every hour (or 30 minutes after successful PCEA dose) + PCEA (5 mL bolus, 10 minute lockout) (n = 31)</td>
<td></td>
<td>Low risk</td>
</tr>
<tr>
<td>Lim et al.</td>
<td>60</td>
<td>Nulliparous</td>
<td>Fentanyl, 25 µg</td>
<td>Levobupivacaine, 0.1%; fentanyl, 2 µg/mL</td>
<td>10 mL/h (n = 30)</td>
<td>5 mL bolus every 30 minutes (n = 30)</td>
<td></td>
<td>Low risk</td>
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<tr>
<td>Lim et al.</td>
<td>50</td>
<td>Nulliparous</td>
<td>Ropivacaine, 2 mg; fentanyl, 15 µg</td>
<td>Ropivacaine 0.1%; fentanyl 2 µg/mL</td>
<td>10 mL/h (n = 25)</td>
<td>2.5 mL every 15 minutes (initiated 7.5 minutes after SA dose) (n = 25)</td>
<td></td>
<td>Low risk</td>
</tr>
<tr>
<td>Salim et al.</td>
<td>127</td>
<td>Nulliparous</td>
<td>N/A</td>
<td>Bupivacaine, 0.125%–0.25%; fentanyl, 2 µg/mL</td>
<td>8 mL/h (0.125%) + PCEA (3 mL bolus, 20 minute lockout) (n = 63)</td>
<td>10 mL bolus every hour (0.25%) (n = 64)</td>
<td></td>
<td>Low risk</td>
</tr>
<tr>
<td>Sia et al.</td>
<td>42</td>
<td>Nulliparous</td>
<td>Ropivacaine, 2 mg; fentanyl, 15 µg</td>
<td>Ropivacaine, 0.1%; fentanyl, 2 µg/mL</td>
<td>5 mL/h + PCEA (5 mL bolus, 10 minute lockout) (n = 21)</td>
<td>5 mL bolus every hour (or 1 hour after successful PCEA dose) (n = 21)</td>
<td></td>
<td>Low risk</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>126</td>
<td>Parous</td>
<td>Bupivacaine, 1.25 mg; fentanyl, 15 µg</td>
<td>Bupivacaine, 0.625%; fentanyl 2 µg/mL</td>
<td>12 mL/h + PCEA (5 mL bolus, 10 minute lockout) (n = 63)</td>
<td>6 mL bolus every 30 minutes + PCEA (5 mL bolus, 10 minute lockout) (n = 63)</td>
<td></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

CEI = continuous epidural infusion; IEB = intermittent epidural bolus; PCEA = patient-controlled epidural analgesia; SA = subarachnoid.
*Reported as an inclusion criteria.

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What study translates well into our setting?

A randomized comparison of automated intermittent mandatory boluses with a basal infusion in combination with patient-controlled epidural analgesia for labor and delivery

S. Leo, C.E. Ocampo, Y. Lim, A.T. Sia
Department of Women’s Anaesthesia, KK Women’s and Children’s Hospital, Singapore

- 0.1% ropivacaine and 2 µg/ml fentanyl
- PCEA: 5 ml bolus, 10 min lockout
  - CEI group: 5 ml/hr
  - Bolus group: 5 ml Q60 min, starting at T=30 min
- Lower LA consumption
- Time to first analgesic request extended from 104 to 268 minutes in bolus group
- 23% of bolus group needed no further supplementation
- Associated with improved satisfaction

![Graph showing time to first PCEA bolus](image-url)
Why did we not opt for a PIEB approach?
A randomised comparison of variable-frequency automated mandatory boluses with a basal infusion for patient-controlled epidural analgesia during labour and delivery

A. T. Sia, S. Leo and C. E. Ocampo

- Mandatory bolus dosing interval adjusted according to previous patient demands
  - Can activate 1-4 times/hr

- Associated with:
  - Less breakthrough pain
  - Less clinician interventions
  - Improved maternal satisfaction
Other additives of note: Clonidine

• Neuraxial clonidine: $\alpha_2$ agonist: dorsal horn spinal cord, reduces release of substance P, increases ACh levels in CSF

• Labour: significant decrease in local anaesthetic consumption, PCEA requirements, improved maternal satisfaction
  • May be of use in opioid dependent women

• But: increased maternal hypotension (requiring treatment), potential increase in instrumental deliveries

• Optimal dosing:
  • Bolus: 60-75 µg (minimal efficacy <60 µg, more side effects >75 µg)
  • PCEA regimens: 1-1.5 µg /ml

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Bazin et al 2011 Anaesthesia
Other additives of note: neostigmine

Epidural Neostigmine versus Fentanyl to Decrease Bupivacaine Use in Patient-controlled Epidural Analgesia during Labor

A Randomized, Double-blind, Controlled Study

Jessica L. Booth, M.D., Vernon H. Ross, M.D., Kenneth E. Nelson, M.D., Lynnette Harris, B.S.N. James C. Eisenach, M.D., Peter H. Pan, M.D.

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Booth et al Anesthesiology 2017
Other additives of note: neostigmine

#OBSIG18

Booth et al Anesthesiology 2017
## Table 3: Duration of Analgesia, Number of Patients Not Needing Epidural Analgesia and Hourly Ropivacaine Consumption in Patients Treated with Intrathecal Ropivacaine/Sufentanil Combined with Epidural Saline (P group) or Epidural Neostigmine/Clonidine (NC group)

<table>
<thead>
<tr>
<th>Duration to Request for Additional Analgesia (min)</th>
<th>P group (n = 35)</th>
<th>NC group (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95 (70–120)</td>
<td>144 (105–163)*</td>
</tr>
<tr>
<td>Number of Patients Delivered Before Epidural Analgesia Was Needed</td>
<td>2</td>
<td>9*</td>
</tr>
<tr>
<td>Ropivacaine Consumption (mg/h)</td>
<td>12.7 (9.6–16.9)</td>
<td>7.5 (3.0–11.9)*</td>
</tr>
</tbody>
</table>

Data are mean ± SD, median and interquartile range or numbers; *P < 0.05 P group vs. NC group.

<table>
<thead>
<tr>
<th>Neostigmine and Clonidine Group (NC)</th>
<th>Placebo group (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hourly ropivacaine use (mg)</td>
<td>11.6 ± 4.2*</td>
</tr>
<tr>
<td>Episodes of Breakthrough Pain, n (%)</td>
<td>3 (6)*</td>
</tr>
<tr>
<td>VAS satisfaction at 1 h (mm)</td>
<td>97 ± 5*</td>
</tr>
<tr>
<td>VAS satisfaction at 24 h (mm)</td>
<td>92 ± 10</td>
</tr>
<tr>
<td>VAS Pain Score at Breakthrough Episodes (mm)</td>
<td>37 ± 23</td>
</tr>
<tr>
<td>Mean Duration of Epidural Analgesia (min)</td>
<td>254 ± 147</td>
</tr>
</tbody>
</table>

*P < 0.05 P group vs. NC group.
How does the KEMH protocol rate?

- PCEA: CADD Solis pump 😂
  - Local anaesthetic: 0.0625% bupivacaine 😏
  - Opioid additive: 2.5 µg /ml fentanyl 😇
  - Other additives: clonidine (rare) 😞
- Bolus volume: 10 ml 😐
- Lockout interval: 20 mins 😝
- Background: 5 ml continuous infusion 😞 😐
How does the KEMH protocol rate?
Summary

• With the dynamic and variable nature of labour pain, epidural analgesia needs to have inherent flexibility to allow for changing requirements.

• PCEA techniques are considered current best practice:
  • Optimal combination of bolus volume and lockout interval are yet to be determined.

• The addition of a background epidural infusion has some potential benefits but also some adverse effects:
  • Changing to a background bolus technique is likely to confer some benefit.

• Epidural clonidine and neostigmine may have advantages in selected circumstances—they may be potentially under-utilized.

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Early versus late labour

3 X increase in MLAC during labour

Capogna et al. BJA 1998

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Induced versus spontaneous labour

**Spontaneous Labor**
- Effective
- Ineffective

**Induced Labor**
- Effective
- Ineffective

Fig. 1. Minimum analgesic dose of sufentanil in spontaneous labor was 21.2 µg (95% CI 19.6, 22.8).

Fig. 2. Minimum analgesic dose of sufentanil in induced labor was 27.3 µg (95% CI 23.8, 30.9).

Capogna et al. Anesth 2001
What bolus parameters?

**The Effect of Manipulation of the Programmed Intermittent Bolus Time Interval and Injection Volume on Total Drug Use for Labor Epidural Analgesia: A Randomized Controlled Trial**

Cynthia A. Wong, MD, Robert J. McCarthy, PharmD, and Bradley Hewlett, MD

190 women: Bupivacine 0.0625%/fentanyl 1.95 mcg/ml
PCEA: 5 ml/ 10 min lockout
PIB: 2.5 ml/15 min or 5 ml/30 min or 10 ml/60 min

**Results**: lower overall LA consumption in 10ml group, no other differences between groups