Multimodal Analgesic Options to Minimize Post-Cesarean Pain

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Disclosure
- DepoDur™
- SkyePharma, Inc.
- Endo Pharmaceuticals
- EKR Therapeutics
- On-Q PainBuster®
- I-Flow

Modern Trends: Cesarean Section

Maternal mortality rate,* by year — United States
*Per 100,000 live births.

True grit: The mum who delivered her own baby
Ines Ramirez Perez and her son Orlando Ruiz Ramirez, 4, gesture in their home in the town of Rio Talea, Mexico. In March 2000, Ines cut open her womb with a kitchen knife her husband used to slaughter animals and delivered Orlando in her rural home after problems developed during labour.

International Journal of Gynecology and Obstetrics
Patient Preferences for Anesthesia Outcomes Associated with Cesarean Delivery


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rank</th>
<th>Relative Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain During Cesarean</td>
<td>8.4  ± 2.2</td>
<td>27 ± 18</td>
</tr>
<tr>
<td>Pain After Cesarean</td>
<td>8.3  ± 1.8</td>
<td>18 ± 10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7.8  ± 1.5</td>
<td>12 ± 7</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.8  ± 1.7</td>
<td>11 ± 7</td>
</tr>
<tr>
<td>Cramping</td>
<td>6.0  ± 1.9</td>
<td>10 ± 8</td>
</tr>
<tr>
<td>Itching</td>
<td>5.6  ± 2.1</td>
<td>9 ± 8</td>
</tr>
<tr>
<td>Shivering</td>
<td>4.6  ± 1.7</td>
<td>6 ± 6</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4.1  ± 1.9</td>
<td>5 ± 4</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2.9  ± 1.4</td>
<td>3 ± 3</td>
</tr>
</tbody>
</table>

Benefits of Postoperative Analgesia

• Improves functional recovery and sleep
• Less DVT and shorter hospital stay
• Breastfeeding success
• Maternal interaction with newborn
• ↓ Chronic persistent post-cesarean pain

Incidence: ± 10%


Opioids Post-Cesarean

Paech MJ et al. Anesthesiology 1994
Harrison. Anesthesiology 1988; 68: 454-7
Intrathecal Opioids Post-Cesarean

Time to first analgesic

Hours Post Spinal

Bupivacaine + IT Morphine
Bupivacaine + IT Fentanyl
Bupivacaine

Dose of Neuraxial Morphine

- Analgesic ceiling, dose-related side effects
- Intrathecal: 50-200 mcg
- Epidural: 2-4 mg

EREM (DepoDur®) Post-Cesarean
Total Narcotic Medication Usage
0 - 48 h (IV MS equivalents in mg)

EREM 10 mg vs. Epidural Morphine 4 mg
Single-dose, post-delivery
Carvalho. Anesth Analg 2007; 105: 176-83

EREM 10 mg

Morphine
Carvalho et al. Anesth Analg 2005; 100: 1150-8
*p<0.05
**EREM (DepoDur®) Post-Cesarean**

*Limited Use*

- Epidural or CSE only
- Side-effects
- Respiratory depression
- Cost
- Familiarity
- Marketing
- Potential local anesthetic interaction


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**Oral Opioids vs. Intravenous PCA Post-Cesarean**

- **Oxycodone-acetaminophen**
  (5/325 mg) 1 to 2 tablets vs.
- **Morphine PCA**
  1 mg, 6 min lock-out, 1 mg/h background

- Less pain at 6 and 24 h
- Less nausea and drowsiness at 6 h


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**NSAIDs Post-Cesarean**

- Numerous post-CS studies show analgesic and opioid-sparing advantage
  1
- Naproxen, indomethacin, diclofenac, ketorolac, tenoxicam, ketoprofen (NNT 1.8-2.7)
  2
- Opioid sparing: 30 - 50%
  3
- ↓ Opoid-related SEs (vomit, sedation ↓ 30%)
  4
- Low breast milk transfer: RID = 0.2-0.6
  5

2. http://www.jr2.ox.ac.uk/bandolier/

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**Acetaminophen**

- 10 - 20% opioid-sparing effect
  1
- COX-3 activity
  2
- Synergistic with oral opioids
- Additive effect than NSAIDs alone
  3
- IV preparation
  4
- Good side-effect profile

1. Remy. BJA 2005;94(4):505-513
Local Anesthetic Wound Infiltration

- Varying analgesic success reported
- Wound and peritoneal spraying
- Some benefits after cesarean under general anesthesia
- Minimal benefit post-cesarean under spinal anesthesia


Long-Acting Local Anesthetics

Local infiltration and nerve blocks

- Microspheres
- Uni and/or multi-layered Liposomes
- Multi-chambered Liposomes

Continuous Local Anesthetic Wound Instillation


- Disposable pumps
- ↓ Opioid use and rescue analgesia
- Reduced pain scores on activity
- Rate 2-5 ml/h

Wound Instillation of Local Anesthetics

Subcutaneous vs. Subfascial

- Multiorifice catheter
- Inserted by surgeon
- Ropivacaine 5 ml/h for 48 h Between unclosed parietal peritoneum and transversalis fascia

Intraperitoneal lidocaine reduces cesarean pain
Multimodal Wound Infiltration

Lavand’homme. Anesthesiology 2007; 106: 1220-5

Incisional Wound Nociceptive and Inflammatory Biochemical Mediator Release Following Cesarean Delivery


Transversus Abdominis Plane Block
Blind Technique

Costello et al. RAPM 2009;34,(6).

TAP Block: Ultrasound-Guided

Costello et al. RAPM 2009;34,(6).
**TAP Block: Ultrasound-Guided**

- Needles
- External oblique muscle
- Internal oblique muscle
- Transversus abdominis muscle

**TAP Block Post-Cesarean**

**No Intrathecal Morphine**

- Spinal anesthetic (bupivacaine + fentanyl)
- Diclofenac and acetaminophen

**Blind Technique**

- 24 hours post-CS:
  - ↓ Morphine use (18 vs. 32 mg)
  - ↑ Satisfaction (96 vs. 77 mm)
  - ↓ Antiemetics

**Ultrasound-Guided**

- McDonnell, Anesth Analg 2006;106:186-91

**TAB Block Post-Cesarean**

**With IT morphine**

- 50 patients per group for 48 h
- 20 ml ropivacaine 0.375% (per side) vs. saline control
- Morphine for breakthrough pain

**TAB Block: Indications**

**Routine Use**

- vs.

**Selected Patients**

(e.g. GA, midline incision, opioid-dependent, no NSAIDs / opioid)

**Breakthrough Pain**

Limited duration unless catheter-based
Reduces incisinal not deep visceral pain

**TAP Block Vs. IT Morphine**

- TAP (bupivacaine 0.375%) vs. IT morphine 200 mcg
- Multimodal analgesic (NSAIDs, acetaminophen)
- **Intrathecal morphine**
  - Superior post-cesarean analgesia at cost of increased opioid-related side effects
  - Visceral (cramping) and somatic (wound) pain

Kanazi et al. Anesth Analg 2010

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**Opioid Side-Effects**

**IT Morphine for Cesarean Delivery**

- **Pruritus**: Incidence 40-90%, dose-dependent
- **Nausea and Vomiting**: 20-30%
- **Respiratory Depression**:
  - Very low incidence $1: \pm 3-500$ (mild) → $1: \pm 2-5000$
  - Neuraxial opioids benefits far outweigh risks
  - Risk not increased compared to IV opioids

Carvalho B. Anesth Analg. 2008; 107: 956-61

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**Gabapentin / Pregabalin**

**The Good**

- **Gabapentin**: Analgesic and opioid-sparing acute postoperative period $^1$
- **Pregabalin**: Dose-related reduction in postoperative opioid $^2$

**Cesarean Delivery:** $^3$

- Single-dose, 600 mg
- Chronic pain similar

2. Zhang et al. BJA 2011; 106: 454-62

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**Gabapentin**

*The Bad*

- **Pre-delivery:** Mean (SD) umbilical vein to maternal vein ratio: 0.86 (0.12) \(^1\)
- **Breastfeeding:**
  - Relative infant dose: 2.34% \(^2\)
- **Maternal side-effects:** Sedation \(^3\)

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2. Kristensen et al. J Hum Lact 2006; 22(4)

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**Ketamine**

- Subanesthetic doses of ketamine reduce opioid use for 24 h after surgery \(^1\)
- **Effective:** 0.15 mg/kg IV during general or spinal anesthesia for cesarean \(^2,3\)
- **Not effective:** 10 mg IV after cesarean with spinal and multimodal analgesia \(^4\)

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1. Bell RF, Cochrane Review 2006:CD004603
2. Keshish P. Anesthesiology 2006;104:27.
4. Bauchat et al. IJJOA 2011; 20: 3-9

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**Ketamine Effect on Postoperative Pain**

**Preoperative Temporal Summation**

- Evaluates CNS sensitization and nociceptive hyperexcitability

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**Targeted or Individualized Treatment Plans**

- **Stratify patients**
- Dosage adjustments or tailor treatment around patient’s needs
- Pain modifying agents (e.g. gabapentin ketamine, clonidine)
- **Early intervention**
- **Resource allocation**
Predicting Post-Cesarean Pain and Analgesic Use

Current Knowledge

- **Demographic, psychological and surgical factors:**
  Younger, anxious, depressed, neurotic, preoperative pain, poor fetal outcome
- **Experimental pain tests** are promising
- **Genetics of postoperative pain** disappointing
- No prediction test or model has been developed for routine clinical use
- Severe acute postoperative pain is associated with chronic pain

Post-Cesarean Analgesia

**Summary**

- No “wonder drug” → Multi-modal approach
- **Standard Management:**
  - IT or EPI Morphine
  - NSAIDS + Acetaminophen
  - Oral opioids for breakthrough pain
- **Additional Medication:**
  - TAP blocks and LA instillation
  - EREM and adjuvants (Gabapentin)
- **Individualized Treatment Plans**

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Cox-2 Inhibitors: Celecoxib

- Cox-2 analgesic efficacy similar to non-selective NSAIDs
- Celecoxib pain relief NNT: 4.2 (200 mg) and 2.5 (400 mg)
- No difference in pruritus and analgesia (secondary endpoint)
- Breast Milk Transfer: RID = 0.3%


Neuraxial Adjuvants

- Clonidine, Neostigmine, Etc.
- Modest analgesic prolongation
- Side-effects and toxicity limit routine use
- Fetal concerns
- Decrease pain sensitization and “wind-up” → persistent post-operative pain