Neuropathic pain after cesarean section: myth or reality?

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Chronic pain

- Female (40%) > Male (31%)
  - IASP Clinical Update 2003

- 20% of patients implicated surgery
  - $\rightarrow$ 50% sole cause
    - Macrae 2001

- Acute postoperative pain
  - $\rightarrow$ 10-50% persistent pain
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Estimated incidence of chronic pain</th>
<th>Estimated chronic severe (disabling) pain (&gt;5 out of score of 10)</th>
<th>US surgical volumes (1000s)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>30–50%</td>
<td>5–10%</td>
<td>159 (lower limb only)</td>
</tr>
<tr>
<td>Breast surgery (lumpectomy and mastectomy)</td>
<td>20–30%</td>
<td>5–10%</td>
<td>479</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>30–40%</td>
<td>10%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Inguinal hernia repair</td>
<td>10%</td>
<td>2–4%</td>
<td>609</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>30–50%</td>
<td>5–10%</td>
<td>598</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>10%</td>
<td>4%</td>
<td>220</td>
</tr>
</tbody>
</table>

*Gall bladder surgery not included, since preoperative diagnosis of pain specifically from gall bladder is difficult and persistent postoperative pain could therefore be related to other intra-abdominal disorders. †National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

**Table 1: Estimated incidence of chronic postoperative pain and disability after selected surgical procedures**

Kehlet Lancet 2006;367:1618-25
Chronic pain: definition
Macrae 2001

- The pain developed after a surgical procedure
- The pain is of at least 2 months duration
- Other causes for the pain should have been excluded (e.g. continuing malignancy or chronic infection)
- The possibility that the pain is continuing from a preexisting problem must be explored and exclusion attempted
- CS: non-cyclic pain (not in relation with hormonal variations)
Chronic pelvic pain

- 15-25% females 30-50 years
  - Gynecological surgery (92%)
  - Hysterectomy (36%)
    - Weijenborg 2007
  - Cesarean section (67.2%)
    - Almeida 2002
Chronic pain following Caesarean section

L. Nikolajsen¹, H.C. Sørensen², T.S. Jensen³ and H. Kehlet⁴
Departments of ¹Anesthesiology and ²Gynaecology and Obstetrics, Viborg Hospital, ³Danish Pain Research Center, University of Aarhus, and ⁴Department of Surgical Gastroenterology, Hvidovre Hospital, University of Copenhagen, Denmark

- 244 patients
- 18% continued to have pain > 3 months after CS
- 12.3% → still had pain 10 months after surgery
  → with almost 4% of them having constant pain
Does magnesium sulfate reduce the short- and long-term requirements for pain relief after caesarean delivery? A double-blind placebo-controlled trial

Michael J. Paech, DM, Everett F. Magann, MD, Dorota A. Doherty, PhD, Lisa J. Verity, MBBS, John P. Newnham, MD


- 120 patients - spinal anesthesia

- Determine if Mg Sulfate decreases postoperative pain and analgesics consumption

- 16% of patients → persisting wound or abdominal pain at 6 weeks
92 patients - spinal anesthesia

48h continuous intrawound infusion with diclofenac, ropivacaine or saline + PCA morphine

Average incidence of 12% of residual pain at 6 months for the 3 groups
Postoperative Analgesic and Antihyperalgesic Effects of Spinal Clonidine administered during elective Cesarean section

P.M. Lavand’homme, F. Roelants, h. Waterloos, V. Collet, M. De Kock

- 96 patients - spinal anesthesia
- Evaluated the postoperative antihyperalgesic effect of spinal clonidine
- Average incidence of residual pain:
  - 14% at 3 months
  - 7% at 6 months
Pain After Delivery (PAD) Study

Pan P ASA Meeting 2007 A 1203

- 4 medical institutions located in NC and NY, USA, Geneva and Brussels
- 2518 patients enrolled, 1861 evaluable
- 9.2% residual pain at 8 weeks after CS
  - Site of incision and back
  - 50%: pain affecting at least 1 or more daily activities (walking, mood, sleep, relations to others or ability to concentrate)
Real problem…

- CS = the most common major surgical procedure in the world
- Incidence $\uparrow$ in developed and developing world $\approx 20\text{-}25\%$
  - 1937 $\rightarrow$ 3%
  - 1990 $\rightarrow$ 12%
  - 2000 $\rightarrow$ 20-25% in US, UK
  - 2007 $\rightarrow$ 20% in France
  - 29.2% in Switzerland (2004)
Real problem...

- To have an exact idea of the problem, we have to consider the number of procedure

- US → 1.1 million CS (2002)
  - 5% chronic pain affecting at least 1 or more daily activities → 55 000 women

- Switzerland → 72 000 births (2003)
  - 20 000 Cesarean Section
  - 1000 women with chronic pain
Persistent postsurgical pain

- Resembles to neuropathic pain
- Continuous inflammatory response can contribute to a maintained inflammatory pain
Release of inflammatory mediators

Peripheral sensitization
- Dorsal root ganglia
  - Neurochemical changes
  - Neuronal loss
  - Ectopic discharge
- Hyperexcitability, change in circuitry, loss of inhibition
- Allodynia, hyperalgesia, spontaneous pain

Central sensitization
- Spinal cord
  - Neurochemical changes
  - Neuronal cell death
  - Sprouting of sensory AB fibres into lamina II

Nerve damage
- CGRP
- SP
- SOM
- VIP
- PACAP
- GAL (CCK)
- NPY
- CCK (VIP)
- PACAP (GAL)
Differentiation of causes

- Neuropathic versus non-neuropathic

  ↓

- Patient’s description of the pain

  To differentiate neuropathic pain from inflammatory pain
<table>
<thead>
<tr>
<th></th>
<th>Neuropathic pain</th>
<th>Inflammatory pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive symptoms and signs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous pain in damaged area</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Heat hyperalgesia</td>
<td>Rarely</td>
<td>Often</td>
</tr>
<tr>
<td>Cold allodynia</td>
<td>Often</td>
<td>Rarely</td>
</tr>
<tr>
<td>Hyperpathia (increased threshold and explosive suprathreshold pains)</td>
<td>Often</td>
<td>Never</td>
</tr>
<tr>
<td>Aftersensations</td>
<td>Often</td>
<td>Rarely</td>
</tr>
<tr>
<td>Paroxysms</td>
<td>Often</td>
<td>Rarely</td>
</tr>
<tr>
<td>Burning pain</td>
<td>Rarely</td>
<td>Often</td>
</tr>
<tr>
<td>Throbbing pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Negative symptoms and signs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory loss in damaged nerve territory</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Motor deficit in damaged nerve territory</td>
<td>Often</td>
<td>No</td>
</tr>
</tbody>
</table>

**Table 2: Characteristic features of neuropathic and inflammatory pain**
Other possible causes of postoperative chronic pain after CS

- Anatomic distortion of pelvic structures
- Adhesions involving bladder, round ligaments and adjacent structures
- Myofascial pain due to nerve bundle injury and formation of neuromas (site incision)

Almeida 2002
Fig. 1. Diagram of the major peripheral nerves that can be involved in chronic groin pain related to obstetric and gynecologic surgery.

Persistent pain: risk factors

- Severity of postoperative acute pain
- Type of anesthesia
- Surgical technique
- Genetic susceptibility
- Preceding pain
- Psychosocial factors
- Others

Postoperative

Intraoperative

Preoperative
Acute postoperative pain
= The most prominent factor

- Association between the intensity of acute postoperative pain and subsequent development of chronic pain after surgery

- Nikolajsen: higher recall of severe postoperative pain when persistent pain
  » Acta Anaesthesiol Scand 2004

- PAD study: 16.5% of operative-deliveries reported having severe postpartum pain ($\geq 7/10$) while in hospital
  » Landau R ASA Meeting 2007 A662
PAD study

*Pan P ASA Meeting 2007 A 1203*

Figure 3. Interrelationships among delivery variables (mode of delivery and acute postpartum pain) and the 8 week outcomes (persistent pain and depression scores).
Persistent pain: risk factors

- Severity of postoperative acute pain
  - Postoperative
- Type of anesthesia
  - Intraoperative
- Surgical technique
- Genetic susceptibility
- Preceding pain
- Psychosocial factors
- Others
  - Preoperative
Type of Anesthesia

- General > Spinal anesthesia
  - Noxious inputs reaching the CNS are less during spinal anesthesia than during general anesthesia
    » Nikolajsen Acta Anaesthesiol Scand 2004

- Insufficient anesthesia and need of additional analgesia or GA
  » PAD study Landau R ASA Meeting 2007 A662
Persistent pain: risk factors

- Severity of postoperative acute pain
- Type of anesthesia
- Surgical technique
- Genetic susceptibility
- Preceding pain
- Psychosocial factors
- Others

Postoperative

Intraoperative

Preoperative
Surgical technique

- Frequency of chronic pain much higher after major operations (major nerve damage)

- Type of incision:
  - The length of Pfannenstiel incision (signs of nerve entrapment)
    » Luijendijk Ann Surg 1997
  - Non-closure of both visceral and parietal peritoneum (↓ postoperative pain)
    » Rafique Br J Obstet Gynaecol 2002
  - Midline incision vs Pfannenstiel: No!
Persistent pain: risk factors

- Severity of postoperative acute pain (Postoperative)
- Type of anesthesia
- Surgical technique (Intraoperative)
- Genetic susceptibility
- Preceding pain
- Psychosocial factors
- Others (Preoperative)
Genetic susceptibility

- Sensitivity to physiological nociceptive and clinical pain

- Differential heritable susceptibility
  - Generation and experience of pain
  - Response to analgesics
Persistent pain: risk factors

- Severity of postoperative acute pain

- Type of anesthesia
- Surgical technique

- Genetic susceptibility
- Preceding pain
- Psychosocial factors
- Others

Postoperative

Intraoperative

Preoperative
Preceding Pain

- Previous pain correlates with the development of chronic neuropathic pain
Persistent pain: risk factors

- Severity of postoperative acute pain
- Type of anesthesia
- Surgical technique
- Genetic susceptibility
- Preceding pain
- Psychosocial factors
- Others

Postoperative
Intraoperative
Preoperative
Psychosocial factors

- Expectation of pain
- Fear, anxiety
- Past memories
- Social environment
- Work and level of activities

Pain is the result of an interaction between biological and psychological variables
Persistent pain: risk factors

- Severity of postoperative acute pain
- Type of anesthesia
- Surgical technique
- Genetic susceptibility
- Preceding pain
- Psychosocial factors
- Others

Postoperative
Intraoperative
Preoperative
Other factors < PAD study

Pan P ASA Meeting 2007 A 1203

- Patients at risk of chronic postpartum pain
  - Pain with menstruation
  - Cesarean section for dystocia
Studies designed to try to prevent persistent pain

Does magnesium sulfate reduce the short- and long-term requirements for pain relief after caesarean delivery? A double-blind placebo-controlled trial

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Postoperative Analgesic Effects of Continuous Wound Infiltration with Diclofenac after Elective Cesarean Delivery

Patricia M. Lavand’homme, M.D., Ph.D., Fabienne Roelants, M.D., Hilde Waterloos, R.N., Marc F. De Kock, M.D., Ph.D.

Postoperative Analgesic and Antihyperalgesic Effects of Spinal Clonidine administered during elective Cesarean section

P.M. Lavand’homme, F. Roelants, h. Waterloos, V. Collet, M. De Kock

Anesthesiology 2007; 106:1220–5

Anesthesia Analgesia 2008 In Press
Mg Sulfate = antagonist of NMDA receptor in the spinal cord

- Alters pain processing
- ↓ induction and maintenance of central sensitization from nociceptive stimulation

Implication:
- prevention of persistent pain?
Spinal injection: 0.5% hyperbaric bupi+ 15µg fentanyl
120 patients - 3 groups- IV magnesium sulfate

<table>
<thead>
<tr>
<th>Groups</th>
<th>Loading dose</th>
<th>after</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td>50mg/kg</td>
<td>2g/h</td>
<td>42</td>
</tr>
<tr>
<td>Low dose</td>
<td>25 mg/kg</td>
<td>1g/h</td>
<td>38</td>
</tr>
<tr>
<td>Control</td>
<td>saline</td>
<td>saline</td>
<td>40</td>
</tr>
</tbody>
</table>

All solutions commenced 1h before surgery and continued for 24h
No effects on early postoperative opioid requirement or pain after CS

Figure  Cumulative meperidine dose ≤48 hours postoperatively. Mg, Magnesium sulfate.
Results

- 8% → punctate mechanical hyperalgesia (von Frey filaments)

- 16% → persistent wound or abdominal pain at 6 weeks
  - low severity (no analgesics)
  - no difference between the groups
Conclusions

- Mg Sulfate does not reduce the severity of short- and long-term pain after cesarean delivery
Explore different analgesic regimens covering the entire perioperative period:

- Systemic opioids - NSAID$_S$
- Continuous wound irrigation with LA:
  - relieve pain by direct inhibition of noxious impulses from the site of injury
- Continuous wound irrigation with NSAID$_S$:
  - ↓ local expression of mediators (PGs) that sensitize nociceptors on afferent fibers
Secondary goal

- Impact on:
  - Prevention of central sensitization
  - Persistent pain at 1-6 months after surgery
Spinal anesthesia – 0.5% hyperbaric bupivacaine + sufentanil

All patients received the same total dose of diclofenac
Fig. 1. Postoperative use for intravenous patient-controlled analgesia (PCA). Cumulative doses of morphine delivered by PCA device at 12, 24, and 48 h after surgery. * P < 0.05 with saline group. Data are expressed as mean ± SD. Treatment groups: [Graph and Table with legend: Saline, Ropivacaine, Diclofenac]
Analgesics benefits of either subcutaneous ropi or diclofenac infusion on the parietal or visceral pain did not extend beyond 24 h after the surgical procedure.
Residual pain at 6 months

<table>
<thead>
<tr>
<th>Group</th>
<th>23%</th>
<th>3%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ropi</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The difference was not significant
Conclusions

- Results suggest the presence of peripheral analgesic properties of diclofenac
- No effect on persistent pain
Postoperative Analgesic and Antihyperalgesic Effects of Spinal Clonidine administered during elective Cesarean section

P.M. Lavand’homme, F. Roelants, h. Waterloos, V. Collet, M. De Kock
Anesthesia Analgesia 2008 In Press

- Spinal clonidine added to spinal bupi and μ-opioid agonist → improvement of analgesia
- $\alpha_2$-adrenoceptor agonists also possess antihyperalgesic properties
- Hyperalgesia after tissue incision:
  - participates to postop pain
  - = clinical expression of central nervous system sensitization induced by nociceptive inputs from the surgical wound

Severe postop pain
Central sensitization

Likelihood to development of persistent pain after surgery
0.5 % hyperbaric bupivacaine = « bupi »

<table>
<thead>
<tr>
<th></th>
<th>Group BS</th>
<th>Group BSC</th>
<th>Group BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>30</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>Spinal injection</td>
<td>Bupi Suf</td>
<td>Bupi Suf Clonidine 75 µg</td>
<td>Bupi Clonidine 150 µg</td>
</tr>
</tbody>
</table>
BC, BSC used less IV morphine during the first 12 hours
Incidence of persistent pain

<table>
<thead>
<tr>
<th></th>
<th>BS</th>
<th>BSC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 3 months</td>
<td>17%</td>
<td>12%</td>
<td>3%</td>
</tr>
</tbody>
</table>

The difference was not significant
Conclusions

- Spinal clonidine 150 µg reduces:
  - development
  - extent
  - incidence

- Despite its antihyperalgesic effect, this dose of clonidine displays only a short-lasting postoperative analgesia

Despite its antihyperalgesic effect, this dose of clonidine displays only a short-lasting postoperative analgesia.
General Conclusions

- Chronic pain after CS is a **Reality**:
  - 10 % → persistent pain
    - ↓ 5 % → severe pain (affecting daily activities)

- But need for further studies

  - Risk factors
    - unrelieved acute postoperative pain
    - insufficient intraoperative analgesia

- Intensified long term multimodal analgesia

- Focus attention to the immediate postpartum period
  (↓ acute suffering and persistent morbidity)
Future…

– Identify subjects at risk
– Develop strategies of prevention in high risk patients

Development of tools allowing to predict patient at risk (greater pain sensitivity)

*Preoperative assessments of pain responses to a nociceptive stimulation
  early postoperative pain responses
*The intensity of early postoperative pain
  development of chronic postoperative pain
*Genetics polymorphism:
  predisposition or not to chronic pain
  reaction to treatment affected or not