Parecoxib, Celecoxib and Paracetamol for Post Caesarean Analgesia: A Randomised Controlled Trial

McDonnell NJ, Paech MJ, Baber C, Nathan E

Clinical Associate Professor Nolan McDonnell
School of Medicine and Pharmacology, School of Women’s and Infants Health
University of Western Australia
and
Department of Anaesthesia and Pain Medicine
King Edward Memorial Hospital for Women
Conflict of Interest

- Study funded through investigator initiated grant from Pfizer
- Pfizer has had no involvement in the study:
  - Design
  - Conduct
  - Analysis
  - Reporting
Introduction

• Caesarean delivery is one of the most commonly performed operations
  – Approx 110,000 per year Aust/NZ
  – Limited evidence base for many aspects of care

• Paracetamol and anti-inflammatories commonly used:
  – Opioid sparing
  – Low cost (oral)
  – High acceptability
Introduction

• Paracetamol:
  – Use is almost routine unless C/I
  – Little evidence of benefit in caesars
    • 3 small studies, mixed results
  – IV formulations now widely available
    • Cost
  – 2g IV loading dose utilised, PK information available
Introduction

- Anti-inflammatories:
  - Traditional NSAIDs widely studied
    - IV formulations “available” (ketorolac, diclofenac, ibuprofen)
  - COX-2 specific agents:
    - Only one published study in this setting: stopped early
    - IV COX-2 agent (parecoxib) available and probably widely used
      - Cost
      - No post caesarean studies to date
Aim

“To determine the analgesic efficacy of paracetamol and parexocib/celecoxb in the first 24 hours post caesarean delivery”
Methods

• Design: randomised, parallel group, double blind, double dummy, placebo controlled trial

• Location: King Edward Memorial Hospital for Women, Perth
  – Feb 2010 to Feb 2012
  – State obstetric referral hospital
  – 6200 deliveries per annum

• Setting: Elective caesarean delivery

• Ethical approval: Women’s and Newborn Health Service
  – Written informed consent

• Registered with ANZCTRN (ANZCTRN 12611000345987)
Methods

• **Inclusion**
  - ASA 1 or 2
  - Elective caesarean
  - Consent to CSE/pethidine PCEA

• **Exclusion**
  - Current opioid medication
  - Contraindication to any of the study drugs
  - Failure to achieve adequate spinal anaesthesia
  - Failure to place epidural catheter
  - Unintentional dural puncture (Tuohy)
  - Conversion to GA
Methods
Randomisation and Blinding

- Randomised by hospital pharmacy into one of four groups
- Pharmacy prepared coded packages of study drugs
  - Packages contained active or placebo medications of identical appearance
    - IV paracetamol or placebo (200 ml)
    - IV parecoxib or placebo (2 ml)
    - Oral paracetamol or placebo capsules
    - Oral celecoxib or placebo capsules
  - All participants, anaesthetists, investigators and staff involved in the care of the participant were blinded to group allocation
Methods

Group Allocation

Group C (Control)
IV Saline placebos
Placebo capsules

Group PC (Parecoxib/Celecoxib)
IV Parecoxib 40 mg (OT)
Celecoxib 400 mg PO at 12 hrs

Group PA (Paracetamol)
IV Paracetamol 2g (200 ml) (OT)
Paracetamol 1g PO at 6/12/18 hr

Group PCPA (Parecoxib/Paracetamol)
IV Paracetamol 2g (200 ml) (OT)
IV Parecoxib 40mg (2 ml) (OT)
Paracetamol 1g PO at 6/12/18 hr
Celecoxib 400 mg PO at 12 hrs
Methods

Standardised anaesthesia and post operative pain relief

• Anaesthesia:
  – Combined spinal-epidural anaesthesia
    • Hyperbaric bupivacaine 0.5% 2.1-2.5 ml and fentanyl 15 mcg
  – Stepwise approach to manage any intra-operative pain
    • IV fentanyl, nitrous oxide, local anaesthetic (epidural or wound)

• Post operative care:
  – Post operative pethidine PCEA 20 mg (4ml) bolus, 15 min lockout
  – Tramadol 50-100 mg PO Q 2 hr PRN for supplemental analgesia
  – Hospital protocol for PONV and pruritus
Methods
Assessments

- Baseline demographics
- 24 hour cumulative PCEA consumption
- Pain (rest & movement 0-10 NRS) at 6, 12, 18 and 24 hours
- Nausea, sedation, pruritus
- Anti-emetic and analgesic supplementation
- Quality of Recovery and Opioid Symptom Distress scores
- Modified Brief Pain Inventory
Statistical Methods

• Primary Endpoint:
  – 25% reduction in 24 hour pethidine PCEA use

• Sample Size:
  – Alpha 0.05, Beta 0.80
  – Mean pethidine use 360mg +/- 122 mg (Paech et al 1994)
  – 26 patients per group
    • Expanded to 30 per group to allow for drop outs
  – a-priori power of 99% to detect 2 point change in dynamic pain

• Analysis:
  – Intention to treat
  – Univariate comparison continuous outcomes: Kruskal-Wallis test
    • Pair wise comparisons: Bonferroni corrections to maintain alpha 0.05
  – AUC for pain/sedation scores in first 24 hours
  – p<0.05 consider statistically significant
Results
Enrolment
Assessed for eligibility: n=537
Recruited: n=144

Excluded
n=6 (surgery rescheduled)
n=27 (failed spinal, failed CSE, dural puncture, conversion to GA)

Randomised n=111

Group C
Allocated n=23
Loss to follow up: n=0
Analysed n=23
Protocol violations n=3
<24hr PCEA n=1

Group PC
Allocated n=30
Loss to follow up: n=0
Analysed n=30
Protocol violations n=4
<24hr PCEA n=2

Group PA
Allocated n=32
Loss to follow up: n=0
Analysed n=32
Protocol violations n=9
<24hr PCEA n=6

Group PCPA
Allocated n=26
Loss to follow up: n=0
Analysed n=26
Protocol violations n=3
<24hr PCEA n=3
## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Group C n=23</th>
<th>Group PC n=30</th>
<th>Group PA n=32</th>
<th>Group PCPA n=26</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>30 [28-25]</td>
<td>30 [26-35]</td>
<td>31 [28-34]</td>
<td>31 [27-34]</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>31 [27-38]</td>
<td>33 [29-38]</td>
<td>32 [29-40]</td>
<td>34 [27-38]</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Previous caesarean</strong></td>
<td>74%</td>
<td>77%</td>
<td>84%</td>
<td>85%</td>
<td>0.71</td>
</tr>
</tbody>
</table>
## Results

### Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Group C n=23</th>
<th>Group PC n=30</th>
<th>Group PA n=32</th>
<th>Group PCPA n=26</th>
<th>p</th>
</tr>
</thead>
</table>
24 hr Area Under the Curve pain scores

* p=0.02
Pain scores at rest

* p=0.017
Pain scores with movement
## Results

### Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Group C n=23</th>
<th>Group PC n=30</th>
<th>Group PA n=32</th>
<th>Group PCPA n=26</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol required</td>
<td>48%</td>
<td>70%</td>
<td>58%</td>
<td>23%</td>
<td>0.004</td>
</tr>
<tr>
<td>Tramadol dose (mg)</td>
<td>0 [0-200]</td>
<td>100 [0-200]</td>
<td>75 [0-200]</td>
<td>0 [0-25]</td>
<td>0.013</td>
</tr>
<tr>
<td>Time to first tramadol (hr)</td>
<td>16.2</td>
<td>2.8</td>
<td>8.6</td>
<td>24.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Nausea (Incidence)</td>
<td>9%</td>
<td>10%</td>
<td>19%</td>
<td>15%</td>
<td>0.696</td>
</tr>
<tr>
<td>Sedation (AUC)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>0.981</td>
</tr>
<tr>
<td>Satisfaction (good/excellent)</td>
<td>83%</td>
<td>90%</td>
<td>91%</td>
<td>96%</td>
<td>0.489</td>
</tr>
</tbody>
</table>
# Results

## Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Group C n=23</th>
<th>Group PC n=30</th>
<th>Group PA n=32</th>
<th>Group PCPA n=26</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol required</td>
<td>48%</td>
<td>70%</td>
<td>58%</td>
<td>23%</td>
<td>0.004</td>
</tr>
<tr>
<td>Tramadol dose (mg)</td>
<td>0 [0-200]</td>
<td>100 [0-200]</td>
<td>75 [0-200]</td>
<td>0 [0-25]</td>
<td>0.01</td>
</tr>
<tr>
<td>Time to first tramadol (hr)</td>
<td>16.2</td>
<td>2.8</td>
<td>8.6</td>
<td>24.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Nausea (Incidence)</td>
<td>9%</td>
<td>10%</td>
<td>19%</td>
<td>15%</td>
<td>0.696</td>
</tr>
<tr>
<td>Sedation (AUC)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>0.981</td>
</tr>
<tr>
<td>Satisfaction (good/excellent)</td>
<td>83%</td>
<td>90%</td>
<td>91%</td>
<td>96%</td>
<td>0.489</td>
</tr>
</tbody>
</table>
Results

• No difference in:
  – Anti-emetic use
  – Quality of Recovery scores
  – Opioid Symptom Distress scores
  – Modified Brief Pain Inventory scores
Discussion

• Limited analgesic benefit in the first 24 hours

• Strengths:
  – Design
  – Blinding
  – 2g IV paracetamol loading dose

• Limitations:
  – Limited to first 24 hours post caesarean
  – Pethidine PCEA as primary analgesic technique
    • Ability to generalize to other opioid based techniques
  – Protocol violations
Discussion

Potential explanations of limited efficacy:

**Design**
- Power
- Pethidine PCEA
- Only first 24 hours
- Pain assessment methods

**Conduct**
- Protocol violations
  - per protocol analysis

**Study Drugs**
- Paracetamol
- Parecoxib
  - Limited to single dose
  - Publication bias?
- Celecoxib
  - 200 mg dose
Conclusions

• In this study, the addition of paracetamol and parecoxib/celecoxib did not reduce primary epidural opioid consumption or pain scores in the first 24 hours post caesarean

• The decision whether to add these agents will depend on whether a decreased requirement for supplemental tramadol is considered beneficial

• Further investigation is warranted
  – Effect on pain after initial 24 hours
  – Effect with other opioid administration routes (IT, IV and PO)
  – Head to head comparisons of COX-2 versus traditional NSAIDs
  – Economic advantages of oral over IV preparations
Acknowledgements

• Research midwives: Desiree Cavill and Tracy Bingham
• Pharmacy Clinical Trials Co-ordinator: Antonia Wong
• Senior Registrars: Michael Soares, Rupert Ledger, Melanie Bloor, Ian Maddox, David Law, Richard Kaye
• Nursing and midwifery staff in the Day Surgical Unit, Recovery room and post-natal wards
• Pfizer Pharmaceuticals