The Role of NSAIDs in Postoperative Pain Management

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ACUTE PAIN MANAGEMENT: SCIENTIFIC EVIDENCE
Fourth Edition 2015


Edited by:
Stephan Schug
Greta Palmer
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Jane Trinca
There is Level I evidence for the effectiveness of the following components of multimodal analgesia:

- Regional anaesthesia (peripheral and epidural)
- Paracetamol
- **NSAIDs/Coxibs**
- Alpha-2-Delta Ligands
- Systemic Local Anaesthetics (lignocaine)
- NMDA Receptor antagonists (ketamine, magnesium)
- Alpha-2 Agonists (clonidine/dexmedetomidine)
- Corticosteroids (dexamethasone)

*Please note, not all medications listed here are approved for the stated use*
Adapted from Julius D, Basbaum A. Nature 2001;413:203-10.
PGE$_2$ Increases Peripheral Excitability

30 seconds after application of 1 µM PGE$_2$

3. Nonselective NSAIDs and coxibs are effective analgesics of similar efficacy for acute pain (U) (Level I [Cochrane Review])
Non-opioid analgesics in adults after major surgery: Systematic review with network meta-analysis of randomized trials

V. Martinez, H. Beloeil, E. Marret, D. Fletcher, P. Ravaud and L. Trinquart

* Please note, not all medications listed here are approved for the stated use
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Difference (95% CI)</th>
<th>Morphine</th>
<th>Mean Difference (95% CI)</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>α2 Agonist</td>
<td>-14.6 (-19.9; -9.4)</td>
<td></td>
<td>-3.5 (-9.2; 2.2)</td>
<td></td>
</tr>
<tr>
<td>COX–2 Inhibitor</td>
<td>-13.5 (-16.8; -10.1)</td>
<td></td>
<td>-8.1 (-11.6; -4.6)</td>
<td></td>
</tr>
<tr>
<td>Corticosteroid</td>
<td>-1 (-8.3; 6.3)</td>
<td></td>
<td>-3.4 (-10.9; 4)</td>
<td></td>
</tr>
<tr>
<td>Metamizol</td>
<td>-7.6 (-17; 1.6)</td>
<td></td>
<td>-4.8 (-12.8; 3.1)</td>
<td></td>
</tr>
<tr>
<td>Nefopam</td>
<td>-10.3 (-16.9; -3.7)</td>
<td></td>
<td>-2.8 (-8.6; 2.9)</td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td>-12.9 (-15.1; -10.6)</td>
<td></td>
<td>-5.2 (-7.4; -3.1)</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>-10.5 (-14.1; -6.9)</td>
<td></td>
<td>-2.9 (-6.5; 0.8)</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>-7.4 (-12.7; -2.1)</td>
<td></td>
<td>-1.8 (-6.4; 2.8)</td>
<td></td>
</tr>
<tr>
<td>Nefopam + NSAID</td>
<td>-13.4 (-30.4; 3.4)</td>
<td></td>
<td>0.8 (-14.9; 16.5)</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen + Metamizol</td>
<td>-7 (-22.3; 8.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen + Nefopam</td>
<td>-23.9 (-40.1; -7.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen + NSAID</td>
<td>-22.8 (-31.5; -14)</td>
<td></td>
<td>-12.4 (-21; -3.8)</td>
<td></td>
</tr>
<tr>
<td>Tramadol + Metamizol</td>
<td>-19.8 (-35.4; -4.2)</td>
<td></td>
<td>-7 (-20.5; 6.3)</td>
<td></td>
</tr>
<tr>
<td>Tramado + NSAID</td>
<td>-12.4 (-34; 91)</td>
<td></td>
<td>-10 (-24; 3.8)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Martinez et al. BJA 2017; 118: 22-31.
Preoperative preemptive drug administration for acute postoperative pain: A systematic review and meta-analysis

R.-R. Nir¹,², H. Nahman-Averbuch¹,², R. Moont¹,², E. Sprecher¹,², D. Yarnitsky¹,²

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² Laboratory of Clinical Neurophysiology, The Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

A significant reduction in postoperative analgesic consumption was observed using preoperative administration of nonsteroidal anti-inflammatory drugs (NSAIDs; 95% CI, 0.61 to 0.14; 31 comparisons), chiefly by the COX-2 inhibitors class (95% CI, 0.95 to 0.33; 13 comparisons).

* Please note, not all medications listed here are approved for the stated use.

COX, cyclooxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs.
Which anti-inflammatory compound? Balancing efficacy with adverse effects

Effective pain management

Adverse effects
Limitations with traditional NSAIDs: Combined incidence of gastroduodenal ulcers

5-7 day use in elderly patients

Subjects with ulcer (%)

Placebo (2/120)

Parecoxib (1/116)

Naproxen (9/45)

Ketorolac (38/116)

*Significantly different from placebo and parecoxib; p<0.05

Stoltz et al. Am J Gastroenterol 2002;97:65
Harris et al. Clin Ther 2001;23:1422
# Coxibs vs. Placebo: Blood Loss

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean (mL)</th>
<th>SD (mL)</th>
<th>Total</th>
<th>Mean (mL)</th>
<th>SD (mL)</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreas Meunier 2007</td>
<td>195</td>
<td>88</td>
<td>24</td>
<td>240</td>
<td>96</td>
<td>20</td>
<td>0.6%</td>
<td>-45.00</td>
<td>(-99.86, 9.86)</td>
</tr>
<tr>
<td>Asokumar Buvanendran 2003</td>
<td>111.8</td>
<td>110</td>
<td>33</td>
<td>80.5</td>
<td>56.9</td>
<td>33</td>
<td>1.1%</td>
<td>31.30</td>
<td>(-10.95, 73.55)</td>
</tr>
<tr>
<td>Scott S. Reuben 2008</td>
<td>286</td>
<td>16</td>
<td>91</td>
<td>289</td>
<td>15</td>
<td>94</td>
<td>97.0%</td>
<td>-3.00</td>
<td>(-7.47, 1.47)</td>
</tr>
<tr>
<td>Yu-Min Huang 2008</td>
<td>181</td>
<td>90</td>
<td>40</td>
<td>177</td>
<td>89</td>
<td>40</td>
<td>1.3%</td>
<td>4.00</td>
<td>(-35.22, 43.22)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>188</td>
<td></td>
<td></td>
<td>187</td>
<td></td>
<td>100.0%</td>
<td>-2.81</td>
<td>(-7.21, 1.60)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 4.90, df = 3 (P=0.18); I² = 39%
Test for overall effect Z = 1.25 (P=0.21)

A meta-analysis of trials evaluating the perioperative use of selective COX-2 inhibitors for TKA on blood loss during the first 24 hours after operation.

There was no difference in blood loss during the first 24 hours after operation between groups.

Adapted from Lin et al. The Journal of Arthroplasty Vol. 28 No. 2 2013.
Limitations with Traditional NSAIDS:
acetylsalicylic acid / NSAID Sensitive Asthma

Journal of Allergy and Clinical Immunology – (20 February 2014)

Safety risks for patients with acetylsalicylic acid-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: Meta-analysis of controlled clinical trials

Daniel R. Morales, MBChB
Brian J. Lipworth, MD
Bruce Guthrie, PhD
Cathy Jackson, MD
Peter T. Donnan, PhD
Virginia H. Santiago, MBBM

AERD can lead to respiratory symptoms after exposure to nsNSAIDs (NNH=13), but not coxibs.
(Level I [PRISMA], 14 RCTs, n=426)

Objective

To address whether parecoxib and valdecoxb increased CV risk in noncardiac surgery patients.

Methodology

Pooled post hoc analysis using 2 large datasets: 17 controlled trials of parecoxib for noncardiac studies and 32 studies, including the 17 non-cardiac parecoxib studies plus 15 studies of valdecoxb. The 32-study dataset provided 95% power to detect a twofold increase in the incidence of CV adverse events assuming a placebo group incidence of 1% (estimated from previous study data), and 69% power to detect a twofold increase from a 0.5% incidence.

Results:

Incidence of total CV events for the 17 parecoxib studies was 0.44% (13 of 2,966) in parecoxib recipients and 0.37% (7 of 1,915) in placebo (P > 0.20). In the analysis of 32 studies, the incidence of total CV events was 0.40% (21 of 5,285) in the parecoxib/valdecoxb group compared with 0.50% (16 of 3226) in the placebo group (P > 0.20). No significant differences in the incidence of total or any individual CV event category were observed between the parecoxib or parecoxib/valdecoxb and placebo groups. When stratified by number of baseline CV risk factors, no significant difference in CV events was detected compared with placebo.

“Conclusions: In the largest analysis of the CV risk of cyclooxygenase selective inhibitors or nonsteroidal anti-inflammatory drugs for perioperative pain management, 
parecoxib and valdecoxiib were not found to increase the risk of CV adverse events after noncardiac surgery.”

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis

Steven E. Nissen, M.D., Neville D. Yeomans, M.D., Daniel H. Solomon, M.D., M.P.H., Thomas F. Lüscher, M.D., Peter Libby, M.D., M. Elaine Husni, M.D., David Y. Graham, M.D., Jeffrey S. Borer, M.D., Lisa M. Wisniewski, R.N., Katherine E. Wolski, M.P.H., Qiuqing Wang, M.S., Venu Menon, M.D., Frank Ruschitzka, M.D., Michael Gaffney, Ph.D., Bruce Beckerman, M.D., Manuela F. Berger, M.D., Weihang Bao, Ph.D., and A. Michael Lincoff, M.D., for the PRECISION Trial Investigators*

On-treatment analysis, a primary outcome event occurred in 134 patients in the celecoxib group (1.7%), 144 patients in the naproxen group (1.8%), and 155 patients in the ibuprofen group (1.9%) (hazard ratio for celecoxib vs. naproxen, 0.90; 95% CI, 0.71 to 1.15; hazard ratio for celecoxib vs. ibuprofen, 0.81; 95% CI, 0.65 to 1.02; P<0.001 for noninferiority in both comparisons). The risk of gastrointestinal events was significantly lower with celecoxib than with naproxen (P=0.01) or ibuprofen (P=0.002); the risk of renal events was significantly lower with celecoxib than with ibuprofen (P=0.004) but was not significantly lower with celecoxib than with naproxen (P=0.19).
Risk of Acute Kidney Injury with NSAIDs and COX-2 Inhibitors

Conclusions: This study provides evidence that risk of AKI may be lower with more selective agents than with naproxen or other non-selective NSAIDs.
# Low Incidence of Adverse Events with Parecoxib

## Table. Frequency of Prespecified Safety Events in 28 Randomized, Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Risk</th>
<th>(# of Patients)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parecoxib</td>
<td>Placebo</td>
</tr>
<tr>
<td>Severe cutaneous adverse reaction</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Embolic and thrombotic event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Venous</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Mixed or unspecified</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>GI ulceration-related event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Perforation</td>
<td>0.0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Ulceration</td>
<td>0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Renal failure and impairment</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylactic</td>
<td>8.7</td>
<td>8.6</td>
</tr>
<tr>
<td>Angioedema</td>
<td>2.6</td>
<td>3.0</td>
</tr>
<tr>
<td>Allergy</td>
<td>&lt;0.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Severe hypotension</td>
<td>2.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Masking signs of inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and soft tissue infections</td>
<td>0.0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Incision site infection</td>
<td>&lt;0.1</td>
<td>0.0</td>
</tr>
</tbody>
</table>

CI = Confidence interval; GI = Gastrointestinal; RR = Relative risk.

Coxibs vs. nsNSAIDs in Postop Pain
(Summary of Key Messages of APM: SE 4th Edition 2015)

- **Blood loss and bleeding complications:**
  - nsNSAIDs > placebo (Level I)
  - Coxibs = placebo (Level I)
  - Coxibs < nsNSAIDs (Level II)

- **GI ulceration short-term (5–7 days):**
  - nsNSAIDs >> placebo (Level II)
  - Coxibs = placebo (Level I)
  - Coxibs << nsNSAIDs (Level II)

- **Bronchospasm in aspirin sensitive asthma**
  - Coxibs = placebo (Level I)
  - nsNSAIDs > Coxibs (Level I)

- **Acute kidney injury**
  - Coxibs = placebo (Level III-2)
  - Coxibs < nsNSAIDs (Level III-2)

- **Cardiovascular complications short-term (5–7 days)**
  - Parecoxib / celecoxib = placebo (Level I)
Conclusions

- NSAIDs (selective and non-selective ones) are an important component of multimodal analgesia
- Coxibs are at least as effective as non-selective NSAIDs
- Preoperative administration and combination with paracetamol increases the efficacy of nsNSAIDs and Coxibs in postoperative pain treatment

- Coxibs are significantly safer than nsNSAID
  - GI ulceration
  - Blood loss
  - Bronchospasm
- Coxibs have no increased risk of
  - Cardiovascular complications
  - Renal complications

ANZCA&FPMANZCA