Effect of celecoxib combined with thoracic epidural analgesia on pain after thoracotomy

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Key points
• Thoracotomy is associated with severe postoperative pain. It can lead to postoperative morbidity.
• TEA is superior to i.v. opioid analgesia, but can be associated with significant postoperative pain.
• The trial tested the ability of 3 days of oral celecoxib to improve analgesia after thoracotomy.
• Celecoxib reduced pain scores without increased morbidity. It might provide useful supplemental analgesic modality.

Background. Thoracotomy results in severe postoperative pain potentially leading to chronic pain. We investigated the potential benefits of oral celecoxib on postoperative analgesia combined with thoracic epidural analgesia (TEA).

Methods. Forty patients undergoing thoracotomy were included in this prospective, randomized, double-blind, placebo-controlled study. General anaesthesia was standardized. Patient-controlled epidural analgesia (T4–T5) was used during 48 h after surgery (ropivacaine 2 mg ml−1 with sufentanil 0.5 μg ml−1). Patients were allocated to receive oral celecoxib or placebo from the evening before surgery until 48 h after operation. Postoperative pain scores, respiratory function, and morbidity were compared between the two groups.

Results. Postoperative pain scores at rest (P = 0.026) and during coughing (P = 0.021) were lower and patient satisfaction was greater (P = 0.0033) in the celecoxib group. Consumption of the local anaesthetic solution was comparable between groups. Postoperative restrictive pulmonary syndrome and morbidity were comparable between groups.

Conclusions. Celecoxib improves postoperative analgesia provided by TEA after thoracotomy.

Keywords: analgesia, epidural, postoperative, cyclooxygenase-2 inhibitor; postoperative outcome, respiratory function; surgery, thoracotomy
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Thoracotomy is one of the most painful surgical procedures. Thoracic epidural analgesia (TEA) provides superior pain relief to i.v. opioid. However, despite TEA, some patients still complain of significant discomfort such as shoulder pain or pain related to chest tubes.

Adequate postoperative analgesia might improve patient outcome and affect the incidence of chronic post-thoracotomy pain. Non-steroidal anti-inflammatory drugs (NSAIDs) are very effective postoperative analgesics. There exist few data concerning the combination of NSAIDs with epidural analgesia after thoracic surgery. The use of perioperative NSAIDs raises the issue of postoperative excessive bleeding. Specific cyclooxygenase-2 (COX-2) inhibitors provide similar postoperative analgesia to non-specific NSAIDs but do not increase the risk of bleeding. However, the potential benefit of COX-2 inhibitor associated with TEA for thoracic surgery has never been investigated. We therefore tested the hypothesis that perioperative celecoxib improves postoperative analgesia provided by TEA after thoracic surgery.

Methods
After approval from the Institutional Ethic Committee at CHU de Liège (Liège, Belgium, N° 2001-61), 40 ASA II–III patients undergoing lung surgery with posterolateral thoracotomy consented to be included in this prospective randomized placebo-controlled study between October 2001 and September 2002. Exclusion criteria were: age <18 yr, renal or hepatic insufficiency, allergy to NSAIDs or aspirin, asthma, history of chronic pain, recent gastroduodenal ulcer, coagulopathy, and recent use of opioids, NSAIDs, or steroid <10 days before surgery.
Protocol
Subjects were randomly allocated in two groups (n=20 in each group). Randomization sequence was predetermined by computer generation. In the celecoxib group, subjects were given 200 mg oral celecoxib (Celebrex®, Pfizer SA, Brussels, Belgium) the evening before surgery, the morning before surgery, and then twice a day for 48 h after operation. In the control group, subjects received placebo tablets at the same time points.

After 6 h n.p.o., all subjects were premedicated with 50 mg hydroxyzine and 0.5 mg alprazolam p.o. 90 min before surgery. In the operating theatre, an i.v. infusion of 10 ml kg⁻¹ of Ringer’s lactate solution was started and an epidural catheter was inserted at the T4–T5 interspace. After an epidural test dose of 3 ml lidocaine 10 mg ml⁻¹ with epinephrine 10 µg ml⁻¹, 5 ml ropivacaine 2.5 mg ml⁻¹ was administered epidurally before the induction of general anaesthesia, followed by a continuous infusion of 5 ml h⁻¹ during surgery. An additional bolus of 5 ml ropivacaine 2.5 mg ml⁻¹ was injected during chest closure. General anaesthesia was induced and maintained with an i.v. infusion of 0.2 µg kg⁻¹ min⁻¹ remifentanil and a target-controlled infusion of propofol adjusted to keep the bispectral index (Aspect Medical Systems, Norwood, MA, USA) around 50. Muscle relaxation was provided with rocuronium 0.6 mg kg⁻¹ to facilitate the placement of a double-lumen endobronchial tube, and the lungs were ventilated with a mixture of 50% oxygen/air.

After arrival in the post-anaesthesia care unit (PACU), postoperative analgesia was provided to all subjects with a patient-controlled epidural analgesia (PCEA) pump using a combination of ropivacaine 2 mg ml⁻¹ and sufentanil 0.5 µg ml⁻¹ by continuous infusion at 3 ml h⁻¹, bolus 3 ml, and lockout interval 20 min. PCEA was maintained until the morning of the third postoperative day. Since the aim of the study was to investigate the effect of celecoxib on epidural analgesia, only subjects with effective epidural analgesia assessed using thermosensory testing in the PACU were included in the study. In addition, all subjects were given 2 g propacetamol i.v., a precursor of acetaminophen (Pro-dafalgan®, UPSAMEDICA Brussels, Belgium; 2 g propacetamol=1 g acetaminophen) every 6 h. In the case of inadequate analgesia [pain scores at rest >30 on a 100 mm visual analogue scale (VAS)], 100 mg tramadol i.v. (Contramal®, Grünenthal, Woluwe-Saint-Etienne, Belgium) was given as rescue medication every 6 h.

Measurements
Pain scores at rest and during coughing and mobilization (moving from the lying to the sitting position) were measured on a 100 mm VAS on admission to the PACU, 4 h after surgery and three times a day on postoperative days 1 and 2. Subject satisfaction with postoperative analgesia was assessed on a 100 mm VAS at the end of the second postoperative day (0, totally dissatisfied; 100, totally satisfied). Epidural local anaesthetic consumption was also recorded.

Bleeding through chest tubes was measured, and blood haemoglobin and plasma, urea, creatinine and troponin-T concentrations were assayed after operation. The incidence of postoperative nausea and vomiting and urinary retention were also recorded.

Pulmonary function [forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and peak expiratory flow rate] was tested before operation and twice a day during the first three postoperative days after chest physiotherapy using a portable spirometer (Spirobank®, MIR, Rome, Italy). Selected postoperative complications were prospectively noted: fever (core temperature >38°C), pneumonia diagnosed clinically and by culture and chest radiography, myocaridal ischaemia defined as a change in the ECG with an elevation of troponin-T above 0.03 µg litre⁻¹, supraventricular arrhythmia, bleeding through chest tubes, need for homologous transfusion, and renal insufficiency defined as an increase in plasma creatinine concentration >20% of baseline.

Statistical analysis
Data are expressed as mean (SD). Student’s t-test, ANOVA for repeated measures, or the Mann–Whitney test was used for quantitative data. Fischer exact test was used to compare qualitative data (SPSS for Windows 12.0). A value of P<0.05 was considered significant. The results of a pilot study in our institution indicated that 17 subjects per group allowed detection of a 20 mm reduction in VAS pain score during coughing assessed on the morning of the first postoperative day with α=0.05 and a 80% power.

Results
Two subjects in each group were excluded because of early unintentional removal of epidural catheter. Data from 36 subjects were used for analysis. Subject characteristics and types of surgery were similar in the two groups (Table 1). The consumption of the ropivacaine/sufentanil mixture and the need for rescue medication (tramadol) were not significantly different between the two groups (Table 2). Pain scores were significantly lower at rest (P=0.026) and on coughing (P=0.021) in the celecoxib group when compared with the control group (Fig. 1a and b). Pain scores during mobilization were also less in the celecoxib group but the

Table 1 Patient characteristic data, type of surgery, and intraoperative remifentanil consumption. Data are median (range), mean (SD), or numbers

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>59 [19–79]</td>
<td>59 [37–78]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70 (12)</td>
<td>67 (14)</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>11/7</td>
<td>12/6</td>
</tr>
<tr>
<td>ASA II/III</td>
<td>6/12</td>
<td>7/11</td>
</tr>
<tr>
<td>Intraoperative remifentanil (mg)</td>
<td>2.3 (0.9)</td>
<td>2.5 (1.0)</td>
</tr>
<tr>
<td>Type of surgery: lobectomy/ pneumectomy</td>
<td>14/4</td>
<td>14/4</td>
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difference was not statistically significant \( (P=0.19) \) (Fig. 1c).

Satisfaction with postoperative analgesia was significantly \( (P=0.0033) \) greater at postoperative day 2 in the celecoxib group (Table 2). No difference was observed in the incidence of postoperative nausea and vomiting or urinary retention.

FVC and FEV1 significantly deteriorated after surgery, but the reductions in these lung volumes were comparable in the two groups. Peak expiratory flow rate or the ratio between FEV1 and FVC did not differ significantly between the groups after surgery (Table 3).

No patient had postoperative elevation of plasma troponin-T. No difference in postoperative morbidity was observed between the two groups (Table 3).

**Discussion**

This study suggests that perioperative treatment with celecoxib, a selective COX-2 inhibitor, significantly improves postoperative analgesia provided by a thoracic PCEA after thoracotomy for lung resection. As a consequence, patient satisfaction with postoperative analgesia was also greater. Postoperative pulmonary function and morbidity were not affected by treatment with celecoxib. We consider the reduction in pain scores by celecoxib (>15 mm on a 100 mm VAS at several time points) as clinically relevant since pain scores were already low with epidural analgesia in the control group, and it resulted in an improved patient satisfaction.

NSAIDs improve analgesia obtained with i.v. opioids after cardiothoracic surgery.\(^{10}\) Studies on the potential benefit of NSAIDs combined with epidural analgesia for thoracic surgery are rare. In a previous study, Bigler and colleagues\(^5\) used continuous epidural infusion of bupivacaine with morphine for analgesia after thoracotomy, which resulted in almost no pain in the control group, making it difficult to demonstrate any additional effect of the NSAID piroxicam. Although the analgesic and anti-inflammatory effects of NSAIDs are mediated by the inhibition of COX enzymes, NSAIDs ability to block COX-1 and COX-2 and to produce analgesia and anti-inflammatory effects differs.\(^{11}\) In fact, piroxicam seems to be more anti-inflammatory than analgesic.\(^{11}\) Moreover, NSAID administration in the study of Bigler and colleagues was started just before surgery. We initiated celecoxib treatment the day before surgery, which allowed more time for drug distribution to the spinal cord where COX-2 activation contributes to nociception and hyperalgesia after tissue trauma. Nevertheless, the efficiency of preemptive analgesia with NSAIDs remains controversial.\(^{12, 13}\) Our results are similar to those of a study investigating the effect of rofecoxib, a selective COX-2 inhibitor no longer available, on postoperative epidural analgesia after knee replacement surgery in which rofecoxib was begun 24 h before surgery.\(^{14}\)

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**Table 2** In hospital morbidity. Data are mean (so) or number of patients (n). **\( P=0.0033 \)** when compared with placebo.

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Total pleural effusion (ml)</td>
<td>880 (370)</td>
<td>1027 (508)</td>
</tr>
<tr>
<td>Hb decrease (preop.—POD-5 values) (g.100 ml(^{-1}))</td>
<td>1.7 (1.2)</td>
<td>1.3 (0.9)</td>
</tr>
<tr>
<td>Blood transfusion (n)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>↑Urea &gt;20% (n)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>↑Creatinine &gt;20% (n)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Supraventricular arrhythmia (n)</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary infection (n)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Fever &gt;38°C (n)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Ropivacaine–sufentanil epidural solution consumption at 48 h (ml)</td>
<td>268 (84)</td>
<td>282 (78)</td>
</tr>
<tr>
<td>Total tramadol consumption at 48 h (mg)</td>
<td>194 (147)</td>
<td>183 (185)</td>
</tr>
<tr>
<td>Patient satisfaction at 48 h (VAS)</td>
<td>85 (16)**</td>
<td>64 (22)</td>
</tr>
<tr>
<td>Postoperative nausea or vomiting (n)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Postoperative urinary retention (n)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hospitalization duration (days)</td>
<td>8.4 (1.2)</td>
<td>8.7 (2.3)</td>
</tr>
<tr>
<td>Intensive care readmission/death (n)</td>
<td>0/0</td>
<td>0/0</td>
</tr>
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</table>

**Fig 1** Pain scores at rest (A), during coughing (B) and mobilization (C) during the first 48 h after operation measured on a 100 mm VAS. Pain scores were measured at arrival in the PACU, 4 h after surgery, on postoperative days 1 and 2 at 8:00 and 18:00. Data are mean (SEM). Celecoxib group is depicted by the blue histograms, whereas the control group is represented by the green striped histograms.
Intraoperative remifentanil can result in spinal sensitization and postoperative hyperalgesia.\textsuperscript{15} This spinal sensitization results from activation of N-methyl D-aspartate receptors in spinal wide dynamic range neurones with activation of COX. The beneficial effect of celecoxib during the early postoperative period might reflect reversal or prevention of this hypersensitization as shown with parecoxib.\textsuperscript{16}

Despite better analgesia, postoperative pulmonary dysfunction is not improved in patients treated with celecoxib. This confirms that pain is not the main determinant of the postoperative pulmonary restrictive syndrome. Complete pain relief obtained with epidural opioids alone fails to reverse this restrictive syndrome; the most effective treatment to reduce the dysfunction is epidural local anaesthetic.\textsuperscript{2} In our study, both groups received epidural ropivacaine at similar doses, so it is not surprising that postoperative pulmonary dysfunction was also similar in both groups.

Contrary to non-selective NSAIDs, COX-2 inhibitors do not increase the risk of bleeding. In this study, pleural bleeding and the postoperative drop in haemoglobin concentration were comparable in the two groups. All NSAIDs can exacerbate the development of renal failure.\textsuperscript{17} In our study, the number of subjects with a postoperative increase in urea and creatinine plasma concentrations was comparable in the two groups. However, our study was not powered to exclude effects on postoperative bleeding and renal function.

Studies have shown a significant increase in coronary acute ischaemic events in patients receiving long-term COX-2 inhibitor treatment.\textsuperscript{18–19} In cardiac surgery patients, the incidence of ischaemic events increased with prolonged postoperative use of parecoxib.\textsuperscript{20} However, in patients undergoing major non-cardiac surgery, 10 days of perioperative administration of valdecoxib–parecoxib did not increase the incidence of major cardiovascular postoperative events compared with placebo.\textsuperscript{21} In our study, administration of celecoxib for 3 days did not result in any ischaemic cardiac events, but it was not powered to test this. The lack of cardiac ischaemic events may be due to the small sample size, the short duration of COX-2 inhibitor administration, and patients’ selection. Indeed, our patients are less likely to have atherosclerotic disease than cardiac surgery patients.

In conclusion, 200 mg celecoxib started the evening before surgery and given twice a day for 48 h after surgery significantly improved the analgesia provided by TEA after thoracotomy with no drug-induced side-effects detected.

**Conflict of interest**

None declared.

**Funding**

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**References**