Single dose parecoxib significantly improves ventilatory function in early extubation coronary artery bypass surgery: a prospective randomized double blind placebo controlled trial

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Background. Parecoxib, a cyclo oxygenase-2 inhibiting non-steroidal anti-inflammatory drug, has been widely used for postoperative analgesia. Our aim was to quantify the benefit of a single dose after coronary artery bypass grafting.

Methods. The investigation was carried out as a randomized double blind placebo controlled study. A single i.v. dose of parecoxib 40 mg or placebo was given at closure of sternotomy. No opioid other than morphine was given in the first 24 postoperative hours. Pain was assessed using both a Visual Analogue Score (1–10), and the amount of morphine used via a morphine patient controlled analgesia pump. Creatinine clearance was measured before and after operation from 24 h urine collections. After a global announcement by Pfizer that paracoxib was ‘contraindicated in patients with ischaemic heart disease’ further recruitment was suspended and the collected data from 40 patients were analysed.

Results. Twenty-one patients received parecoxib and 19 received placebo. Amongst those who received parecoxib, there was a highly significant sparing of rescue medication before tracheal extubation (P=0.004) compared with placebo, and an overall 35% morphine sparing effect during the first 6 h post extubation after correction for the variability in extubation time (P=0.037). Respiration, as measured by arterial carbon dioxide tension at the time of extubation, was significantly better in the parecoxib group (P=0.045). Significantly more furosemide was given for postoperative oliguria in those patients who received parecoxib (P=0.036). After correcting for differences in diuretic usage and fluid balance, parecoxib was associated with a significant increase in plasma creatinine (P=0.041).

Conclusion. A single dose of parecoxib has a significant opioid sparing effect in the first 6 h after coronary artery bypass grafting which resulted in significantly improved ventilation with mild elevation of plasma creatinine within normal limits.

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Introduction

There is no agreed definition of ‘early extubation’ or ‘fast track’ cardiac surgery. However, in our institution there has been a gradual reduction in the duration of elective postoperative ventilation for routine cases. This is attributable to advances in all aspects of patient care and encouraged by a scarcity of intensive care beds. Importantly, ‘early extubation’ reduces Intensive Therapy Unit stay.1,2 In our unit between one-quarter and one-third of elective cases undergo early extubation avoiding admission to intensive care. They
remain intubated, for a short period (typically 40–60 min) and after extubation, are directly transferred to a high dependency area.

Previous use of non-steroidal anti-inflammatory drugs (NSAIDs) in coronary surgery patients is thought to be fairly common although published reports are limited. Whilst beneficial opioid sparing effects (typically 40% opioid sparing in first 24 h) have been demonstrated with indomethacin, none of the studies have specifically considered the value of non-steroidal agents in the immediate peri-extubation period.3–6 No previous study has prospectively evaluated the potential benefit of opioid sparing on ventilatory function during the period of spontaneous ventilation preceding tracheal extubation. Arguably if opioids contribute to postoperative respiratory depression, opioid sparing analgesia should improve ventilatory function and provide earlier recovery. Accordingly our study aimed to test this simple hypothesis.

The use of NSAIDs has long been associated with the risk of renal failure.7,8 Coronary artery bypass surgery itself carries an overall risk of postoperative renal ‘dysfunction’ (raised abnormal creatinine) of around 7.7%, and acute renal failure (requiring dialysis) around 1.4%.9 Previous studies have used estimates of creatinine clearance based on plasma creatinine concentration.10 A measurement of the effect of the systemic inflammatory response to bypass on renal function has previously been based on assay of the markers of renal tubular damage.11,12 Our study measured creatinine clearance to detect any parecoxib effect on renal function. Urinary α1-microglobulin was also measured in an attempt to quantify any effect of the bypass process itself on renal function distinct from any effect of parecoxib.

Parecoxib is a relatively new agent with an improved safety profile in terms of gastrointestinal bleeding which appeared to confer advantages over older drugs.13 Its analgesic efficacy is well documented in other surgical specialities.14–16 However, after prolonged use in cardiac surgical patients it has been associated with impaired wound healing17 and recently, serious thrombotic postoperative complications.18 Whilst the future of ‘coxib’ anti-inflammatory drugs hangs in the balance, our findings have wider implications for the use of all types of NSAIDs in major surgery.

Methods

The study was conducted between July 2003 and January 2005.

Selection of patients

All patients were scheduled for elective coronary artery bypass grafting. They were considered to be low risk cases aged 70 yr or less with good or moderate ventricular function and normal preoperative plasma creatinine. Diabetics, patients on anti coagulants, and those with previous cerebrovascular disease were excluded.

Random allocation into two groups was achieved using a random number generator, and the results placed into consecutively numbered sealed envelopes by a third party not involved in the study. The envelopes were opened at close of surgery also by a third party not involved in the trial. According to instruction they drew up into a syringe, 2 ml of saline (placebo) or 2 ml of parecoxib 40 mg in solution. The unlabelled syringe was then given to the anaesthetist to administer at close of surgery. As a result, the surgeon, anaesthetist and recovery staff did not know who received placebo and who received parecoxib. Patient characteristics data and intercurrent medication are shown in Table 1. Patients stopped taking aspirin 5 days before operation and stopped taking angiotensin converting enzyme inhibitors on the day before surgery.

Surgery

Coronary artery bypass grafting was performed using pulsatile flow cardiopulmonary bypass at 34°C. During aortic cross clamping, the myocardium was protected by antegrade cold blood cardioplegia with repeated intermittent boluses. The left internal mammary artery was harvested in all cases and 25 patients also received radial arterial grafts.

Anaesthesia

Before induction, a 14 g i.v. cannula and a 20 g radial arterial line were inserted. Anaesthesia was induced with etomidate 0.2 mg kg⁻¹, alfentanil 2.5 mg and rocuronium 0.9 mg kg⁻¹ and maintained with isoflurane in an oxygen/air mixture. After tracheal intubation, the right internal jugular vein was cannulated with a 3 lumen central venous catheter and a 7.5 gauge i.v. sheath. All patients received 2 g of i.v. tranexamic acid. Supplemental 0.5 mg boluses of alfentanil were administered intraoperatively as required to maintain the patient’s heart rate and blood pressure close to baseline pre-incision values. All patients received 1 litre of Hartman’s solution and thereafter gelatin in order to maintain a central venous pressure of +6 to +10 mm Hg. All i.v. fluids were administered through a fluid warmer connected to the 7.5 gauge sheath. Patients were rewarmed to a nasopharyngeal temperature of 37°C maintained for 10 min before weaning from bypass. At closure of sternotomy, neuromuscular blocking agent was antagonized with neostigmine and glycopyrrolate and spontaneous ventilation established.

Table 1: Patient characteristics data and routine preoperative medication. The mean (SD) for patient characteristics data and preoperative medications for placebo and parecoxib groups are shown. The two groups are similar in terms of age, weight, EuroSCORE19 and preoperative medications.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Parecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58.8 (6.6)</td>
<td>56.7 (9.1)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.9 (11.5)</td>
<td>80.0 (14.6)</td>
</tr>
<tr>
<td>EuroSCORE19</td>
<td>1.63 (1.61)</td>
<td>0.92 (0.39)</td>
</tr>
<tr>
<td>Beta blockade</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Diuretics</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>7</td>
<td>10</td>
</tr>
</tbody>
</table>
Patients were given a loading dose of morphine 50 μg kg\(^{-1}\) and randomly allocated to receive either a single i.v. dose of parecoxib 40 mg or normal saline (placebo). Patients were then transferred intubated but spontaneously breathing in a supine 45° head up position to the recovery room.

**Postoperative care**

On arrival in the recovery room, our spontaneously breathing patients were transferred to a T-piece attachment providing humidified 60% oxygen. A positive endexpiratory pressure valve was added to the T-piece expiratory limb in order to provide continuous positive airway pressure of 5 cm of water in those patients who remained intubated for longer than 1 h in order to minimize the risk of pulmonary collapse. A heated over blanket was applied in order to keep the patient’s peripheral temperature between 30°C and 32°C and nasopharyngeal temperature greater than 36°C. Postoperative analgesia was administered as soon as patients were able to respond. They were given 2 mg i.v. boluses of morphine (rescue medication) at a minimum of 3 min intervals, at the discretion of the recovery room staff, and until they indicated that they were comfortable. Arterial blood gas analysis was performed on admission to the recovery room and at 30 min intervals up to the point of extubation. After extubation, patients were given a Graseby morphine patient controlled analgesia (PCA) device to self administer 1 mg boluses of morphine with a 5 min lock-out period. Visual analogue pain scoring was commenced at the same time as the morphine PCA. Measurements were recorded for the first 6 h of PCA usage and at 24 h post surgery. Morphine PCA was continued for the first 24 postoperative hours. Postoperative fluid maintenance consisted of i.v. dextrose saline at 0.5 ml kg\(^{-1}\) h\(^{-1}\) with gelatin given as 250 ml boluses to maintain a central venous filling pressure of +6 to +10 mm Hg. Patients were encouraged to commence oral intake as soon as possible. Postoperative hypotension (systolic pressure < 100 mm Hg) was treated initially with fluid therapy to raise central venous filling pressure to 10 mm Hg. Hypotension that persisted was managed with an i.v. infusion of norepinephrine. Oliguria (urine output less than 0.5 ml kg\(^{-1}\) h\(^{-1}\) for greater than 1 h) that persisted after correction of hypovolaemia and or hypotension was treated with an i.v. 40 mg bolus of furosemide. Postoperative nausea was treated with i.v. 4 mg boluses of ondansetron.

Patients were discharged from the recovery unit to our postoperative progressive care unit in the early evening. No other opioids were administered during the first 24 h but all patients received 6 hourly acetaminophen 1 g suppositories. Our unit’s standardized criteria for extubation are shown in Table 2. Aspirin 75 mg was given at 22.00 h on the evening of surgery, and continued daily thereafter.

**Data collection and analysis**

After the patient was admitted to the hospital, a preoperative urine collection was commenced. In the anaesthetic room blood was sampled for plasma creatinine measurement. This was used for the preoperative creatinine clearance calculation. After induction of anaesthesia a 20 ml sample of urine was collected from the urinary catheter for measurement of α-1-microglobulin. A second 24 h urine collection was commenced 24 h postoperation and a urinary α-1-microglobulin measurement made at the same time. The second plasma creatinine measurement occurred 48 h after operation.

I.V. fluid volumes from theatre included i.v. fluid administered by the anaesthetist and also fluid returned after operation from the bypass machine and red cell salvage. Postoperative fluid balance was calculated to include oral and i.v. fluid intake and postoperative urine output and costal drain loss. The change in creatinine before or after operation for each of the two groups was simply calculated as (postoperative – preoperative).

Parametric data described in the study were analysed by Student’s t-test and expressed as mean (standard deviation). χ² analysis was used for qualitative data analysis. Non-parametric data were analysed by Mann-Whitney U-test and expressed as median (range). Extubation time data were additionally subjected to Kaplin-Meier survival analysis. An analysis of covariance was used to correct for differences in extubation time when calculating total morphine usage to 6 h post extubation. Further analyses of covariance were applied to univariate models to analyse the effect of parecoxib on renal function and to analyse the change in urinary α-1-microglobulin.

A sample size of 50 was considered adequate to demonstrate morphine sparing based on similar studies in other patient populations. Taking a significant difference of creatinine clearance of 30 ml min\(^{-1}\) and a standard deviation of 40 ml min\(^{-1}\) a sample size of 58 was required for 80% power of detection. As a result, the total intended sample size was 60 for our primary outcome measures.

After a global announcement by Pfizer that paracoxib was ‘contraindicated in patients with ischaemic heart disease’
further recruitment was suspended and the collected data from 40 patients were analysed.

**Results**

**Patient characteristics data**

The random allocation resulted in 21 patients receiving parecoxib and 19 patients receiving placebo. The study made provision for the exclusion of patients at close of surgery in the event of either anaesthetic or surgical complications. None occurred and no exclusions were made. Patient characteristics data are shown in Table 1. The groups are similar in terms of age, weight, EuroSCORE\(^1\) and preoperative drug therapy. The mean bypass and aortic clamp times and number of grafts for all 40 patients are shown in Table 3.

**Analgesia and tracheal extubation**

Primary study outcome data for analgesia and tracheal extubation are shown in Table 4 and Figure 1. Intraoperative alfentanil usage for the two groups was similar being 6.40 (1.69) mg for the parecoxib group and 6.24 (2.25) mg for the placebo group \((P=0.79)\). The median (range) amount of morphine before extubation was lower in the parecoxib \([0 (0–3) \text{mg}]\) than in the placebo group \([3 (0–16) \text{mg}] \;(P=0.004)\). After correcting for variation in extubation times using an analysis of covariance, the mean total morphine requirement at 6 h post extubation was also lower in the parecoxib group \([0.11 (0.08) \text{mg kg}^{-1}]\) than in the placebo group \([0.17 (0.10) \text{mg kg}^{-1}] \;(P=0.037)\). Visual analogue pain scores at 6 h post extubation were similar in the parecoxib group \([2.07 (1.81) \text{cm}]\) and the placebo group \([2.65 (1.77) \text{cm}] \;(P=0.37)\). All patients in the parecoxib group were extubated within 2 h of surgery \([32 (6–120) \text{min}]\). In the placebo group extubation times ranged from 5 to 277 min with a median of 42 min \((P=0.307)\). However, Kaplin-Meier survival curve analysis (Fig. 1) shows a differing trend in extubation pattern between groups \((P=0.053)\). The mean partial pressure of arterial carbon dioxide at extubation was 0.43 kPa lower in the parecoxib group \((P=0.045)\).

**Fluid therapy and renal function**

During surgery, patients in the parecoxib group received a mean of 4380 (980) ml of fluid whilst patients in the placebo group were similarly given 4390 (1300) ml \((P=0.989)\). Mean bypass times of 75.9 (18.4) and 75.1 (15.7) min were similar in both groups \((P=0.882)\). Urine output intraoperatively did not differ between parecoxib and placebo groups \([749 (399)\text{and} 667 (296)\text{ml}, P=0.470]\). One patient in each group received furosemide intraoperatively. Both groups had mean positive fluid balances at 24 h post surgery. Parecoxib and placebo groups respectively were calculated as being 1350 (1280) ml and 922 (804) ml positive balance \((P=0.209)\). By 48 h post surgery patients in the paracoxib group had a fluid balance of −80 (1630) ml and patients in the placebo group [0.17 (0.10) mg kg\(^{-1}\)] \((P=0.037)\). Visual analogue pain scores at 6 h post extubation were similar in the parecoxib group [2.07 (1.81) cm] and the placebo group [2.65 (1.77) cm] \((P=0.37)\). All patients in the parecoxib group were extubated within 2 h of surgery [32 (6–120) min]. In the placebo group extubation times ranged from 5 to 277 min with a median of 42 min \((P=0.307)\). However, Kaplin-Meier survival curve analysis (Fig. 1) shows a differing trend in extubation pattern between groups \((P=0.053)\). The mean partial pressure of arterial carbon dioxide at extubation was 0.43 kPa lower in the parecoxib group \((P=0.045)\).

![Figure 1](image-url)

**Figure 1** Extubation time post-coronary artery surgery for 40 patients. Extubation times for the 21 patients who received parecoxib (striped) and the 19 patients who received placebo (black) are shown. Both groups show a marked leftward skew in extubation time. Construction of a survival curve (inset) shows a differing trend in extubation pattern \((P=0.053)\) between the two groups.

### Table 3

<table>
<thead>
<tr>
<th>Number of grafts</th>
<th>Number of patients</th>
<th>Bypass time (min)</th>
<th>Aortic clamp time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>56 (42–70)</td>
<td>32 (23.5–40.5)</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>65 (60–70)</td>
<td>40 (37–43)</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>85 (81–89)</td>
<td>47 (44–50)</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>110 (107–113)</td>
<td>64 (59–69)</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th>Morphine (mg)</th>
<th>Morphine (mg kg(^{-1}))</th>
<th>Arterial extubation (P_{\text{ext}}(\text{kPa}))</th>
<th>Exubation time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parecoxib</td>
<td>0 (0–3)</td>
<td>0 (0–0.038)</td>
<td>6.46 (0.57)</td>
</tr>
<tr>
<td>(n=21)</td>
<td></td>
<td></td>
<td>32 (6–120)</td>
</tr>
<tr>
<td>Placebo</td>
<td>3 (0–16)</td>
<td>0.04 (0–0.153)</td>
<td>6.89 (0.65)</td>
</tr>
<tr>
<td>(P=0.209)</td>
<td></td>
<td></td>
<td>42 (5–277)</td>
</tr>
</tbody>
</table>

\(P=0.004\)
the placebo group had a fluid balance of 922 (804) ml
\( (P=0.640) \). Piroximide was administered after operation
for oliguria in 16 patients from the parecoxib group and 9
patients from the placebo group. Diuretic usage in the pare-
coxib group was significantly higher \((P=0.036) \). Mean
plasma creatinine in the parecoxib group increased signifi-
cantly from 83.0 (11.0) \( \mu \text{mol litre}^{-1} \) to 94.4 (13.0)
\( \mu \text{mol litre}^{-1} \) whilst in the placebo group, a mod-
est increase in creatinine from 86.5 (16.4) \( \mu \text{mol litre}^{-1} \) to
88.9 (17.0) \( \mu \text{mol litre}^{-1} \) was not significant \((P=0.645) \). Ana-
lysis of covariance showed a significant \((P=0.041) \) increase
in plasma creatinine attributable to parecoxib remained after
correcting for any differences in fluid balance, baseline cre-
atinine and diuretic usage.

Calculation of creatinine clearance for those patients who
received parecoxib revealed pre- and postoperative values of
102 (31) ml min\(^{-1} \) and 102 (27) ml min\(^{-1} \) which were nearly
identical statistically \((P=0.970) \). Parecoxib patients had pre-
and postoperative creatinine clearances of 90 (39) ml min\(^{-1} \)
and 103 (33) ml min\(^{-1} \) which were similar \((P=0.310) \).

One sample from the placebo group and three samples from
the parecoxib group were spoiled during assay for
urinary \( \alpha \)-1-microglobulin. Both parecoxib and placebo
groups showed highly significant increases in urinary \( \alpha \)-1-
microglobulin concentrations from preoperative values of
7.61 (2.74) mg litre\(^{-1} \) and 8.33 (5.94) mg litre\(^{-1} \) to postoper-
ative values of 27.5 (31.4) mg litre\(^{-1} \) and 33.5
(33.8) mg litre\(^{-1} \) \((P=0.010) \). An analysis of covariance
revealed that the magnitude of \( \alpha \)-1-microglobulin increase
was related to baseline creatinine \((P=0.024) \) but unrelated to
either the magnitude of the creatinine increase or parecoxib
treatment.

Other results

Seven patients who received parecoxib required norepineph-
rine for hypotension after operation compared with eight
patients who received norepinephrine from the placebo
group. No other inotropic support was required.

Mean costal drain loss in the first 24 h was 733 (327) ml
for patients in the parecoxib group and 830 (432) ml for
those patients who received placebo \((P=0.442) \). None of
the 40 patients received blood transfusion or required clot-
ting factor replacement. No patient required re-sternotomy
for bleeding.

One patient in the placebo group sustained a postoperative
embolic stroke in the left posterior inferior cerebellar artery
territory confirmed on coaxial tomography scan. A second
patient in the placebo group required antibiotics for a chest
infection. Both of these patients had extended hospital stays.
The remaining 38 patients were discharged on either the 4th
or 5th postoperative day.

Discussion

Our technique for early extubation in cardiac surgery has
provided a particularly sensitive model for investigating the
clinical effects of parecoxib. The two groups of randomly
allocated patients are well matched in terms of patient char-
acteristics data (Table 1). The uniformity of surgical oper-
ating is well emphasized by the narrow 95\% confidence
intervals of bypass and aortic clamp times for 2, 3 and 4
coronary grafts (Table 3). Intraoperative opioid usage and
fluid therapy were also similar for study and placebo groups.

The sparing of morphine administered before extubation
in the parecoxib patient group is striking. The overall 35\%
reduction in morphine usage at 6 h post extubation is also
important. At close of surgery both groups had a small
loading dose of 50 \( \mu \text{g kg}^{-1} \) of i.v. morphine because the
quantity of alfentanil used for the procedure although
adequate to provide excellent suppression of autonomic
responses intraoperatively is inadequate for postoperative
analgesia. This may have reduced the difference in morphine
consumption between the two groups, but we did not con-
sider it ethical to create a placebo group with no effective
analgesia at close of surgery. The similar morphine con-
sumption between our patient groups at 24 h post surgery
is entirely in keeping with the offset of the analgesic action
of parecoxib.

The reduction in median extubation time from 42 min in
the placebo group to 32 min in the parecoxib group in itself is
not significant. This is a result of the marked skew of the data
with the majority of patients in both groups being extubated
in under 120 min (Fig. 1). However, a Kaplan-Meier survival
analysis reveals a difference of borderline significance in the
overall pattern of extubation with a trend towards more
prolonged intubation in the placebo group (insert Fig. 1).
Importantly, parecoxib group patients have a significantly
reduced arterial carbon dioxide tension at extubation. Given
the reduction in morphine consumed by the parecoxib group
before extubation, and in consideration of the close match-
ing of the two groups in all other aspects, it seems likely that
the improvement in extubation pattern and arterial carbon
dioxide tension represents a genuine improvement in vent-
ilatory function from reduced respiratory depression and
sedation. This would appear attributable to a beneficial
opioid sparing effect of parecoxib.

Demonstration of identical pain scoring in both groups at
6 h post extubation is an important indicator of the quality of
postoperative analgesia. The relatively low pain scores
(around 2/10 cm) at this point also show that both groups
had effective analgesia. Pain scores between groups over the
6 h post extubation period or at 24 h post surgery were sim-
ilar (results not shown).

Engoren and colleagues\(^{20} \) using an opioid based technique
achieved a best mean extubation time of 167 min with a
range from 114 to 400 min excluding 21\% of patients
who required prolonged ventilation because of a variety of
complications. Zybnik and Bruceck\(^{21} \) have published the
most pro active strategy of early extubation with a
large proportion of patients being extubated in theatre or
within 10 min of close of surgery. Comparison with their
work is difficult as they provided no information on
postoperative analgesia and refer to surgery performed without cardiopulmonary bypass. In their group of 160 patients, around 7% had prolonged intubation for a variety of causes. It has previously been proposed that there is an ‘extubation window’ \(^22\) with an optimum time to confirm stability before proceeding whilst avoiding potential complications of prolonged ventilation. Our parecoxib and placebo groups with median extubation times of 32 and 42 min respectively, and no re-intubation or early complications in either group compared favourably with currently cited works. We conclude that our technique of establishing spontaneous ventilation at close but remaining intubated long enough for assessment by our recovery staff represents the best chance of realizing the ‘extubation window’. It would appear that our study selection and inclusion criteria for early extubation surgery are robust.

At the time our study commenced in 2003, our major concerns regarding the use of parecoxib were related to the reported increased incidence of sternal wound breakdown \(^17\) and the risk of nephrotoxicity. In the study by Ott and colleagues, patients who received parecoxib or its oral equivalent had a 3% incidence of sternal wound dehiscence. A ‘creatinine increase’ was also observed to occur more commonly, but it was not significant.

NSAIDs by definition attenuate the inflammatory response, and may cause impaired wound healing as a class specific effect. Sternal wound dehiscence is a serious complication which can lead to mediastinitis. In the study by Ott and colleagues \(^17\) patients up to 77 years of age with type II diabetics and those receiving inotropes were included. These patients may well be at an increased risk of wound dehiscence. More importantly, some of these patients were treated with valdecoxib and parecoxib for 17 days. Our own sample size is too small to detect with any confidence a 3% incidence of sternal wound breakdown. However, diabetics of all types were excluded and our upper age limit was 70. Patients with impaired contractility post bypass would also have been excluded. Most importantly however, our patients were exposed to a single dose of parecoxib with an arguably much reduced risk.

The mechanism of nephrotoxicity of NSAIDs is unknown. It is almost certainly a complex interaction. Inhibition of renal production of the arteriolar vasodilator Prostaglandin E\(_2\) by NSAIDs may impair renal vascular auto regulation. The renal vasconstrictor effects of angiotensin II generated in the normal response to surgery in such circumstances would theoretically be amplified. Prostaglandin E\(_2\) additionally provides some functional antagonism of anti-diuretic hormone. In the presence of a reduced concentration of renal prostaglandin E\(_2\) the increased stress response levels of anti-diuretic hormone generated by surgery would promote increased sodium retention. \(^78\) The combined effect would be a reduction in renal blood flow, and oliguria. This effect would be exacerbated by systemic hypotension, \(^8\) co-administration of angiotensin converting enzyme inhibitors, \(^23\) diuretics \(^24\) and in patients older than 75 yr. \(^25\) Clearly all of these factors may co-exist in the population of cardiac surgical patients. We were careful to limit patient age. Angiotensin converting enzyme inhibitors were discontinued before operation, and systemic hypotension after operation was aggressively treated with norepinephrine according to our protocol.

In our study, mean plasma creatinine and measured creatinine clearance were within normal limits before and after operation for both parecoxib and placebo groups. However, diuretic usage for the treatment of postoperative oliguria was significantly increased in the parecoxib group. Interestingly the parecoxib group patients also showed a significant 11 \(\mu\)mol increase in plasma creatinine concentration from pre- to postsurgery. When adjusting for differences in diuretic usage, fluid balance, and baseline creatinine, a significant effect of parecoxib on creatinine increase remains \((P=0.041)\).

The parecoxib group showed no change in plasma creatinine clearance despite a highly significant creatinine increase. Our explanation is that a transient reversible period of renal hypo-perfusion has occurred after parecoxib administration. This is consistent with our higher incidence of furosemide given for oliguria. In this highly catabolic postoperative period a significant elevation in creatinine could occur. This would subsequently be cleared after the restoration of renal perfusion. Hence an increased plasma creatinine and a normal clearance could co-exist. Clearly this would not represent steady-state conditions, and the role of clearance measurements in the acute perioperative period is possibly less informative than the simple measure of creatinine change. It should however also be appreciated that our study is underpowered to detect changes in clearance of less than 30 ml min\(^{-1}\) as our intended sample size was 60.

Despite these limitations our normal creatinine clearance values of the order of 90–100 ml min\(^{-1}\) are reassuring. They compare favourably with estimated vales in other cardiac surgical patients. \(^12\) Whilst it is clear that single dose parecoxib has not produced any serious alteration in renal function, the effect on plasma creatinine measured 48 h after a single dose is impressive. The risk of nephrotoxicity may well be enhanced by repeated doses and less than rigorous management of fluid balance and hypotension. This finding has implications for the use of NSAIDs in major surgery outside a high dependency setting.

In our study design we were keen to identify any potential renal damage that might result from the inflammatory process of bypass itself rather than from parecoxib. For this reason we measured urinary \(\alpha-1\)-microglobulin release before operation and at 24 h after surgery. Both groups of patients showed a significant increase in these values which compare with other sources. \(^11\) In an analysis of covariance, baseline creatinine was found to have a significant effect on the magnitude of \(\alpha-1\)-microglobulin increase \((P=0.024)\). Neither the creatinine increase nor parecoxib treatment influenced the magnitude of the \(\alpha-1\)-microglobulin increase. An interaction test did not show any combined
effect of parecoxib treatment and baseline creatinine on α1-microglobulin increase.

Whilst α1-microglobulin may be an elegant marker of renal tubular damage by immune complexes, it is likely to be too sensitive to identify clinically significant renal damage. The fact that α1-microglobulin increase is related to baseline creatinine is difficult to explain. It is possible that baseline creatinine itself is a marker for susceptibility to inflammatory damage by the kidneys. There is no published information on the association of α1-microglobulin release with postoperative renal failure. More information on the functional significance of the markers of tubular damage is needed. This may prove to be a difficult question to resolve and our own results suggest that creatinine clearance measurement is unlikely to be sufficiently sensitive in the immediate perioperative period. This is a result of the presence of a non-steady state during the urine collection period. Deferring the postoperative measurement further would possibly negate this but may be too distant from the time of surgery to be meaningful.

The two largest studies using NSAIDs in cardiac patients both reported adverse effects.17 18 The latter study18 was influential in Pfizer’s decision to suspend the use of parecoxib in patients with heart disease. Ott and colleagues17 acknowledge a 20% opioid sparing effect of parecoxib in their patients, however, the data relating to analgesia in this study has previously been questioned.25 Nussmeier and colleagues18 do not identify any clinical benefit of parecoxib or valdecoxib. Parecoxib was given continuously for 3 days followed by 10 days of valdecoxib. The significant finding in this study was two postoperative myocardial infarcts in the study groups (1088 patients) compared with no infarcts in the 548 patient control group and five ‘cardiac arrest or sudden death’ cases in the treatment group. The study includes no overall mortality data. Any clinical benefit from analgesia on improved lung function which may for the sake of argument have resulted in earlier mobilization or a reduced incidence of pneumonia was not considered. The case mix was particularly broad and included a number of high risk patients.

The uncomplicated course of our patients may simply be attributable to patient selection. However, the process of avoiding mechanical ventilation may be beneficial. The lack of myocardial ischaemia as a postoperative complication could be a result of improved cardiac output. The high proportion of arterial grafts used in our patients may also be a contributory factor. The benefits of arterial revascularization in general27 and of radial artery harvest28 in particular are now well recognized. It must however be appreciated that our sample size is too small to detect the relatively infrequent cardiovascular complications referred to by Nussmeier and colleagues. Interestingly, both our complications; a confirmed stroke, and a chest infection occurred in our control group.

Our own limited findings suggest an important benefit on ventilatory function of single dose parecoxib in the immediate postoperative period but highlight the potential for nephrotoxicity of NSAIDs.

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References

analgesia and is opioid-sparing following total hip arthroplasty. 
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