Patients’ Global Evaluation of Analgesia and Safety of Injected Parecoxib for Postoperative Pain: A Quantitative Systematic Review

Peter Kranke, MD*, Astrid M. Morin, MD, DEAA†, Norbert Roewer, MD*, and Leopold H. Eberhart, MD†

*Department of Anesthesiology, University of Würzburg, Germany; and †Department of Anesthesiology, University of Marburg, Germany

Parecoxib is the only parenterally administered cyclooxygenase-2-selective inhibitor available. We performed a systematic review, including full reports of randomized comparisons of parecoxib compared with any other analgesic intervention for prophylaxis or treatment of postoperative pain. Dichotomous data on patients’ global evaluation of their analgesic regimen were extracted by means of the fraction of patients who rated their medication as “good” or “excellent.” For safety analysis, data on any reported adverse effects were extracted. Relative risk (RR), number needed to treat (NNT), or number-needed-to-harm were calculated with 95% confidence intervals (CI). Data from 9 trials of 50 initially screened were finally analyzed. One thousand thirteen patients were randomized to receive parecoxib, 218 patients were allocated to an active control, and 507 patients received a placebo. With prophylactic administration, the pooled NNT to obtain the desired outcome (“good”/“excellent” rating) with parecoxib 20 and 40 mg compared with placebo was 4.5 (RR, 1.42; 95% CI, 0.91–2.24) and 4.0 (RR, 1.40; 95% CI, 1.10–1.79), respectively. In the treatment trials, the NNT to obtain the outcome of interest with parecoxib 20 mg was 2.1 (RR, 3.44; 95% CI, 1.49–7.96), 5.3 (RR, 1.43; 95% CI, 1.01–2.02), and −8.3 (RR, 0.85; 95% CI, 0.75–0.97) for the comparisons with placebo, morphine, and ketorolac, respectively. The corresponding NNT for treatment with parecoxib 40 mg was 1.7 (RR, 4.65; 95% CI, 2.04–10.61), 3.7 (RR, 1.62; 95% CI, 1.21–2.16), and 50 (RR, 1.03; 95% CI, 0.89–1.18) for the comparisons with placebo, morphine, and ketorolac, respectively. Overall adverse effects for parecoxib 20 and 40 mg were not different from those with placebo, morphine, or ketorolac. These results suggest a favorable profile for parecoxib compared with inactive or active controls. The optimal dose, timing, and frequency of administration need to be determined.

(Anesth Analg 2004;99:797–806)
The clinical studies included in this systematic review often involve a basic analgesic regimen that consists of an NSAID or COX-2 inhibitor that is supplemented by unrestricted access to rescue medication—for instance, via self-administered (patient-controlled analgesia; PCA) or nurse-administered pain control with opioids.

The effect of injected parecoxib on pain relief in placebo-controlled trials has been evaluated by using the proportion of patients with at least 50% pain relief over 4 to 6 h (5). Cumulative data on patient-related outcome descriptions are lacking, although this aspect might become more important in obtaining the true value of interventions that should improve patient well-being. The aim of this systematic review was to evaluate the efficacy and harm of parenteral parecoxib versus active comparators or inactive control for the treatment or prophylaxis of postoperative pain by means of patients’ global evaluation with the applied analgesic regimen and the observed incidence of adverse effects.

**Methods**

The study was performed in accordance with the QUORUM statement (Quality of Reporting of Meta-Analyses) for conducting systematic reviews (6). Features not described extensively were comparable to other analyses on related topics of perioperative care (7,8).

Relevant studies were full reports of randomized, double-blinded comparisons of IV or IM injected parecoxib compared with placebo or any other analgesic regimen for acute postoperative pain. Outcomes of interest were patients’ global evaluation of the applied analgesic regimen measured on a four-point Likert scale (“good,” “excellent,” “fair,” or “poor”) or a visual analog scale. Dichotomous data were derived by

1. Using the fraction of patients who rated their analgesic regimen as either good or excellent. In terms of the patients’ global evaluation, this means that the binary outcome of interest was patients who rated the postoperative analgesia “good” or “excellent” as compared with “poor” and “fair.” Patients’ global evaluations of analgesic regimens close to the 24-h observation period were used for further analyses.

2. Using all information on any observed adverse effects as stated by the included articles and on distinct adverse effects as reported in the studies. We analyzed the number of patients with any observed adverse event only if the study reported exactly that outcome. Calculation of “overall adverse events” on the basis of distinctive symptoms may be misleading because of the occurrence of more than one symptom in a single patient.

We searched MEDLINE, EMBASE, CENTRAL within the Cochrane Library, and the Science Citation Index up to June 2003. “Parecoxib” was the free text search term. The German manufacturer of parecoxib (Dynastat®, Pfizer GmbH, Karlsruhe, Germany) was contacted and asked for additional references. All relevant references and review articles were examined for potential additional references.

All retrieved reports were screened by one author. Irrelevant data were excluded at this stage. Potentially relevant reports were then read by at least two other authors to assess the adequacy of randomization, blinding, description of withdrawal, and, finally, scoring according to the validated 3-item, five-point Oxford scale as in previous analyses (9).

We graphically explored the interstudy variability and analyzed the robustness of the results for clinically homogeneous subgroups by using L’Abbé plots. No further statistical testing of heterogeneity was performed because these tests were not helpful (10). Separate analyses were performed for different doses. It was intended to pool IV and IM regimens if no obviously different efficacy could be detected. Repetitive dosing regimens (e.g., overall three or four doses administered in intervals of 12 h) were grouped together with the single- or double-dose regimen because patients’ global evaluation of the study medication was measured within a time interval (24 h) in which even a single dose should exert some analgesic effects, considering the elimination half-life of 8–11 h (11). Furthermore, the restriction of the analysis of the patients’ assessment near 24 h after surgery guarantees that even the studies that used multiple dosing regimens did not administer three or four times the amount of parecoxib as the single-dose prophylaxis study. This approach is useful to answer the question of whether patients have rated parecoxib as good or excellent, but it does not answer the question of how much parecoxib needs to be given in 24 h for patients to rate treatment as good or excellent. Trials that investigated parecoxib given as prophylactic analgesia before the patients’ request and in the subsequent time period at distinct intervals were analyzed separately from trials in which parecoxib was first administered at the patients’ request or if a certain pain level was present.

Data entry and statistical calculations were performed with the computer program Review Manager 4.2, provided by the Cochrane Collaboration. A random-effects model was applied to calculate relative risks (RR) and numbers needed to treat (NNT) with 95% confidence intervals (CI).

**Results**

A search in the electronic databases revealed 50 hits overall. Exclusion of trials that did not match the
inclusion criteria was unambiguous. All trials that were judged relevant on the basis of the information given in the abstract were finally included. The pharmaceutical company did not provide additional relevant references. We eventually analyzed data from nine randomized trials (Table 1). In those trials, including 1738 subjects, 1013 patients had been randomized to receive parecoxib, 218 patients had been allocated to an active control (morphine 4 mg, n = 84; ketorolac 30 and 60 mg, n = 134), and 507 patients had received a placebo. In all trials, access to rescue medication (consisting of NSAIDs or opioids via nurse-administered bolus doses or PCA) was accessible. In six of the nine studies, the medication was administered for prophylaxis (12–17), for instance, during the induction of anesthesia. In the remaining three studies, the study medication (parecoxib versus an active or inactive control) was given as a treatment when there was need for postoperative analgesia. In those cases, medication was usually repeated every 12 h in the subsequent period to constitute the basis of an available regimen of rescue analgesia with NSAIDs or opioids on patient request. Doses of 20 mg (n = 7 trials) and 40 mg (n = 9 trials) of parecoxib were investigated in most of the trials, whereas one study reported efficacy of 80 mg (12). Summary analyses could not be conducted if information was available from only a single small trial or one comparison. This applies to the comparison with a bolus dose of parecoxib 80 mg and some reported adverse events. One trial investigated IM parecoxib (18). The obtained data were analyzed and summarized with the respective dosages given via the IV route. Key study characteristics, including doses, surgical sites, patient characteristics, and quality scores of the reported methodology, are summarized in Table 1.

As indicated in Table 1, 7 of 9 studies had more than 2 treatment arms. For this reason, the number of comparisons included in the analyses exceeds the number of studies included in this systematic review.

Dichotomous data on the patients’ global evaluation of study medication could be obtained from all but one article (15). This article was included for analysis of adverse effects. In one article (16), the patients’ global evaluation with analgesia was assessed when IV administration was changed to oral administration 72 h after the initiation of treatment and for the entire period. Assessment was subsequently repeated, and a range of “excellent” and “good” ratings was presented in the article, but no ratings for distinct time intervals were given. We decided not to exclude the study, because the range was very small, but we further analyzed the presented data assuming a worst-case (i.e., low efficacy of parecoxib) and best-case (i.e., high efficacy of parecoxib) scenario for the assessment of interest because no precise data could be obtained.

All 17 comparisons of IM or IV injected parecoxib versus placebo across all doses and regimens (prophylaxis or treatment) showed better overall patient global evaluations with the study medication (Fig. 1A). In one comparison (14), 20 mg of IV parecoxib, when administered as prophylaxis, was as effective as placebo for yielding the desired outcome (Fig. 1A).

The RR (chance) of yielding a “good” or even “excellent” rating in the patients’ global evaluation was 1.42 (95% CI, 0.91–2.24) and 1.40 (1.10–1.78) (best-case scenario, 1.46 [95% CI, 1.11–1.92]) for 20 and 40 mg of parecoxib versus placebo when administered prophylactically. The results for the pooled data on 40 mg of parecoxib were statistically significant compared with placebo (Table 2). These data indicate that 3.7 to 4 patients need to be treated with prophylactic parecoxib 40 mg for 1 additional patient to rate the analgesic regimen “good” or “excellent” instead of “fair” or “poor” compared with placebo. These efficacy data for the prophylaxis were obtained, with the exception of one trial (12), from a regimen that used the given dose (20 or 40 mg) every 12 h.

If treatment was initiated after an actual need for analgesia, parecoxib treatment was statistically superior compared with placebo in both investigated doses of 20 mg (RR, 3.44; 95% CI, 1.49–7.96) and 40 mg (RR, 4.65; 95% CI, 2.04–10.61). These results of therapeutic 40 vs 20 mg of injected parecoxib could be translated to an NNT of 1.7 and 2.5, respectively, for yielding at least a “good” patient rating in the overall satisfaction assessment (Table 2).

Only two trials were eligible for inclusion that dealt with the comparison of 20 or 40 mg of injected parecoxib versus 4 mg of morphine given as an analgesic treatment. All four comparisons with both investigated doses of parecoxib showed a better effect with parecoxib compared with morphine, and the use of parecoxib was more frequently associated with the desired outcome of interest (“good” or “excellent” patients’ global evaluation of study medication) (Fig. 1B). The RR of 1.43 (95% CI, 1.01–2.02) for 20 mg and 1.62 (95% CI, 1.21–2.16) for 40 mg of parecoxib versus 4 mg of morphine suggests a significant effect of parecoxib and could be translated in the given setting to an NNT of 5.3 and 3.7, respectively (Table 3), indicating that 40 mg of the drug might be more effective.

Although all four comparisons of 20 mg of parecoxib showed less favorable results compared with ketorolac treatment, this was the case in only one comparison that used 40 mg of parecoxib (Fig. 1B). If treatment with parecoxib was compared with 30 or 60 mg of injected ketorolac, the RR of obtaining “good” or “excellent” patient feedback was 0.85 (95% CI, 0.75–0.97) with 20 mg and 1.03 (0.89–1.18) with 40 mg of parecoxib. On the basis of the RR, this means that ketorolac was significantly superior to injected bolus doses of 20 mg of parecoxib, whereas there was
**Table 1. Characteristics of Included Randomized Controlled Trials Investigating Parecoxib for Acute Postoperative Pain**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Oxford Scale</th>
<th>Patients in the inactive control group (n)</th>
<th>Active controls (n)</th>
<th>Patients in the parecoxib group (n)</th>
<th>Dose (mg)</th>
<th>Route</th>
<th>Prophylaxis/treatment</th>
<th>Timing</th>
<th>Prerequisite for initiation of treatment</th>
<th>Age, mean (range)</th>
<th>Body weight, kg mean (range)</th>
<th>Sex (F/M), n</th>
<th>Procedures/duration (min) (anesthesia/operation)</th>
<th>Type of anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desjardins (12)</td>
<td>1/1/1</td>
<td>56</td>
<td>0</td>
<td>40/20/80</td>
<td>IV</td>
<td>IV</td>
<td>Prophylaxis</td>
<td>30-45 min before surgery</td>
<td>NA</td>
<td>23 (18–35)</td>
<td>0</td>
<td>135 /91</td>
<td>Extraction of impacted third molars /10–30 min</td>
<td>0</td>
</tr>
<tr>
<td>Hubbard (13)</td>
<td>2/1/1</td>
<td>63</td>
<td>0</td>
<td>65/20 (&lt;4)/67/40 (&lt;4)</td>
<td>IV</td>
<td>IV</td>
<td>Prophylaxis</td>
<td>End of surgery with repetition every 12 h</td>
<td>NA</td>
<td>69 (43–83)</td>
<td>81 (48–115)</td>
<td>142 /53</td>
<td>Total knee replacement /88 min</td>
<td>Spinal</td>
</tr>
<tr>
<td>Malen (14)</td>
<td>2/1/1</td>
<td>70</td>
<td>0</td>
<td>67/20 (&lt;3)/64/40 (&lt;3)</td>
<td>IV</td>
<td>IV</td>
<td>Prophylaxis</td>
<td>First request for analgesia with repetition every 12 h</td>
<td>Patient request</td>
<td>68 (8)</td>
<td>0</td>
<td>93 /108</td>
<td>Hip arthroplasty</td>
<td>General (73%), spinal (27%)</td>
</tr>
<tr>
<td>Ng (15)</td>
<td>2/2/1</td>
<td>17</td>
<td>0</td>
<td>19/40</td>
<td>IV</td>
<td>IV</td>
<td>Prophylaxis</td>
<td>Induction of anesthesia</td>
<td>NA</td>
<td>43 (9)</td>
<td>69 (8)</td>
<td>36 /0</td>
<td>Abdominal hysterectomy /72 min</td>
<td>General</td>
</tr>
<tr>
<td>Ott (16)</td>
<td>1/1/1</td>
<td>151</td>
<td>0</td>
<td>311/40 (&lt;6)</td>
<td>IV</td>
<td>IV</td>
<td>Prophylaxis</td>
<td>30 min after extubation with repetition every 12 h</td>
<td>Patient request</td>
<td>60 (34–76)</td>
<td>0</td>
<td>62 /400</td>
<td>Coronary artery bypass grafting</td>
<td>General</td>
</tr>
<tr>
<td>Tang (17)</td>
<td>2/2/1</td>
<td>18</td>
<td>0</td>
<td>19/20/40</td>
<td>IV</td>
<td>IV</td>
<td>Prophylaxis</td>
<td>First request for analgesia with repetition every 12 h</td>
<td>Patient request</td>
<td>47 (8)</td>
<td>75 (8)</td>
<td>55 /0</td>
<td>Abdominal hysterectomy (myomectomy)</td>
<td>General</td>
</tr>
<tr>
<td>Barton (23)</td>
<td>1/2/1</td>
<td>42</td>
<td>K etorolac 30 mg</td>
<td>39/20/38</td>
<td>IV</td>
<td>IV</td>
<td>Treatment</td>
<td>&lt;6 h after discontinuation of PCA</td>
<td>VAS &gt;45/50 to severe pain</td>
<td>42 (29–65)</td>
<td>77 (50–135)</td>
<td>202 /0</td>
<td>Abdominal hysterectomy (myomectomy)</td>
<td>General</td>
</tr>
<tr>
<td>Daniels (18)</td>
<td>2/2/1</td>
<td>51</td>
<td>Ketorolac 60 mg</td>
<td>51/20/50</td>
<td>IM</td>
<td>IV</td>
<td>Treatment</td>
<td>&lt;6 h after surgery</td>
<td>VAS &gt;50/60 to severe pain</td>
<td>21 (8)</td>
<td>77 (8)</td>
<td>157 /117</td>
<td>Extraction of impacted third molars</td>
<td>0</td>
</tr>
<tr>
<td>Rasmussen (24)</td>
<td>2/1/1</td>
<td>39</td>
<td>Ketorolac 30 mg</td>
<td>43/20/40</td>
<td>IV</td>
<td>IV</td>
<td>Treatment</td>
<td>&lt;6 h after discontinuation of PCA</td>
<td>VAS &gt;45/50 to severe pain</td>
<td>67 (47–84)</td>
<td>93 (8)</td>
<td>135 /73</td>
<td>Total knee replacement</td>
<td>0</td>
</tr>
</tbody>
</table>

In case of lacking data for the whole population, data represent the mean values for the active (parecoxib) group.

R/B/D = randomization, blinding, dropouts; NA = not applicable/no data available; VAS = visual analog scale ranging from 0 to 100 mm; PCA = patient-controlled analgesia.
Figure 1. L’Abbé plots of trials investigating patients’ global evaluation of study medication with parecoxib versus placebo (A) and morphine or ketorolac (B). Symbols represent the ratios of patient ratings of “good” or “excellent” between parecoxib and control. The line with a 45° slope indicates equality. P = prophylaxis; T = treatment.
Table 2. Pooled Results of Randomized Controlled Trials of Injected Parecoxib Versus Placebo on the Patients’ Global Evaluation of Study Medication

<table>
<thead>
<tr>
<th>Timing</th>
<th>Dose (mg)</th>
<th>Parecoxib-/placebo-treated patients (n)</th>
<th>Relative risk of a “good/excellent” evaluation with treatment versus placebo</th>
<th>NNT</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
<td>20</td>
<td>201/202</td>
<td>1.42 (0.91–2.24)</td>
<td>NNT 1.41</td>
<td>12–14, 17</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>40</td>
<td>506/353</td>
<td>1.40 (1.10–1.79)</td>
<td>NNT 4.0</td>
<td>12–14, 16, 17</td>
</tr>
<tr>
<td>Treatment</td>
<td>20</td>
<td>183/130</td>
<td>3.44 (1.49–7.96)</td>
<td>NNT 2.5</td>
<td>18, 23, 24</td>
</tr>
<tr>
<td>Treatment</td>
<td>40</td>
<td>175/130</td>
<td>4.65 (2.04–10.61)</td>
<td>NNT 1.7</td>
<td>18, 23, 24</td>
</tr>
</tbody>
</table>

Results are given separately for prophylaxis versus treatment and 20 vs 40 mg. Ninety-five percent confidence intervals are given in parentheses. A number needed to treat (NNT) is presented only if there was a significant difference compared with the control group.

Table 3. Pooled Results of Randomized Controlled Trials of Injected Parecoxib Versus 4 mg of Injected Morphine on the Patients’ Global Evaluation of Study Medication

<table>
<thead>
<tr>
<th>Timing</th>
<th>Dose (mg)</th>
<th>Parecoxib-/morphine-treated patients (n)</th>
<th>Relative risk of a “good/excellent” evaluation with treatment versus morphine</th>
<th>NNT</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>20</td>
<td>82/81</td>
<td>1.43 (1.01–2.02)</td>
<td>NNT</td>
<td>23, 24</td>
</tr>
<tr>
<td>Treatment</td>
<td>40</td>
<td>80/83</td>
<td>1.62 (1.21–2.16)</td>
<td>NNT 5.3</td>
<td>23, 24</td>
</tr>
</tbody>
</table>

Results are given separately for 20 vs 40 mg. Ninety-five percent confidence intervals are given in parentheses. A number needed to treat (NNT) is presented only if there was a significant difference compared with the control group.

no significant difference between parecoxib 40 mg and ketorolac 30 or 60 mg. Transferred into NNTs, this means that if approximately eight patients are treated with 20 mg of parecoxib instead of 30 or 60 mg of ketorolac, one will not reach the desired outcome (i.e., rate the analgesic regimen as “fair” or “poor” instead of “good” or “excellent”) who would have rated the analgesic regimen as “good” or “excellent” had he or she received ketorolac. However, the pooled results of 40 mg of parecoxib versus ketorolac showed no difference regarding the patients’ global evaluation of study medication; this indicates equal satisfaction with analgesia (Table 4). Sensitivity analysis with distinct homogeneous comparators showed no difference between 30 mg (RR, 0.86; 95% CI, 0.70–1.06) and 60 mg (RR, 0.85; 95% CI, 0.72–1.00) of ketorolac when compared with 20 mg of parecoxib and between 30 mg (RR, 0.95; 95% CI, 0.65–1.40) and 60 mg (RR, 1.06; 95% CI, 0.94–1.20) of ketorolac when compared with 40 mg of parecoxib. Therefore, data on 30 and 60 mg of ketorolac were pooled and analyzed as active comparators versus parecoxib.

All trials reported some data that could be used for safety analysis to evaluate the balance between efficacy and harm between the investigated interventions. Two main outcomes were extracted: overall incidence of adverse effects and separate adverse effects that were reported in a uniform and dichotomous manner throughout the trials. Pooled results of the extracted data were again presented if more than two different trials were eligible for a specific adverse outcome.

It is of note that all observed effects were analyzed. This does not necessarily mean that all effects were treatment-related. In addition, this could well mean that certain interventions possess additional beneficial effects apart from providing analgesia (for instance, reduced fever or decreased headache).

When the overall incidence of any observed adverse effect was compared between treatment with parecoxib and placebo, there was no difference between groups (Table 5). The same results were obtained if the two investigated dosages of parecoxib were analyzed separately.

The cumulative risks for adverse effects, analyzed in at least two trials, are presented in Table 5. Although there was no statistically significant difference between groups for the occurrence of nausea and vomiting, the parecoxib group had significantly less headache (RR, 0.68; 95% CI, 0.48–0.97) and fever (RR, 0.31; 95% CI, 0.21–0.46). One trial in patients undergoing coronary artery bypass surgery reported a significantly more frequent incidence of sternal wound infection with parecoxib versus placebo and concluded that further data are needed to confirm or disprove this finding (16).

There were fewer reports of adverse effects with parecoxib compared with morphine, but there was no statistically significant difference between groups (RR,
the Patients
one important patient-centered outcome: the patients
randomized trials that used comparable methods and
This quantitative systematic review pooled data from
discussion
0.89; 95% CI, 0.73–1.10). The same applies for somno-
ence, which was less frequent in the parecoxib group,
but without statistical significance (RR, 0.45; 95% CI,
0.11–1.82). Again, the incidence of fever was signifi-
cantly reduced when patients received parecoxib in-
stead of morphine (RR, 0.27; 95% CI, 0.12–0.62).

The incidence of any adverse effect between pare-
coxib and ketorolac across all doses was comparable.
The RR for the cumulative incidence of adverse effects
was 0.93 (95% CI, 0.85–1.01) across all trials and doses
(Table 5). However, as shown with the previous anal-
yses, the incidence of fever was reduced by the ad-
ministration of parecoxib compared with ketorolac
(RR, 0.15; 95% CI, 0.07–0.33). No incidence of other
adverse effects differed significantly between the
parecoxib- and ketorolac-treated patients. Pooled RRs
for the occurrence of distinct adverse effects between
groups are presented in Table 5.

Discussion
This quantitative systematic review pooled data from
randomized trials that used comparable methods and
one important patient-centered outcome: the patients’
global evaluation of study medication. This was as-
essed at distinct comparable time intervals, and anal-
yses are based on the assessment near 24 hours after
the first administration of the investigated analgesic
regimen. All identified trials used the same outcome
on an identical Likert scale (“poor,” “fair,” “good,”
or “excellent”). This makes the data eligible to be
included into a meta-analysis and ensures that homoge-
neous data are pooled and that apples are not com-
pared with oranges.

Together with an analysis of the observed adverse
effects, the patients’ view allows a good approxima-
tion of the balance between benefit and harm. The
main findings of the review are as follows:
1. Patients are more likely to rate the prophylactic
analgesic regimen as “good” or “excellent” when
parecoxib is given compared with placebo and
morphine.
2. With treatment trials, it is easier to show whether
parecoxib works and to differentiate between in-
terventions. In the preventive trials, the fact that
we do not know how much pain, if any, patients
will have after surgery leads to the observed
phenomenon that parecoxib is judged better
when given as treatment. Thus, patients’ global
evaluation with parecoxib compared with placebo is better when patients receive treatment
when they experience acute pain compared with
prophylactic treatment, even though unrestricted
rescue analgesics were guaranteed in all trials.
3. Injected parecoxib (40 mg) can substitute for ke-
torolac 30–60 mg and is equally effective in
terms of patients’ global assessment when it is
used as treatment for postoperative pain.
4. Parecoxib appears not to cause more adverse
effects than placebo and other active analgesics
(i.e., morphine or ketorolac) when used for pro-
phylaxis and treatment.
5. When parecoxib was used for prophylaxis of
postoperative pain, the resulting baseline analge-
ia associated with the use of parecoxib was cor-
related with better patients’ global evaluation.
Interestingly, this was not necessarily correlated
with an obvious decrease of adverse effects in the
parecoxib group (less nausea due to a potential
opioid-sparing effect, for instance).
6. The investigated outcome of patients’ global
evaluation with the study drug and the dichoto-
mous analysis of patients rating the treatment
“good” or “excellent” rather than “fair” or
“poor” seem to be valuable end-points for the
investigated setting and are sensitive for differ-
ences between treatment groups.

Because the statistical technique of combining re-
results from randomized controlled trials in quantita-
tive systematic reviews is well established and because
there are increasingly more articles that use this
method to improve the level of confidence, we focus
on two major issues that arise from this meta-analysis.
Choosing a Relevant Clinical Outcome. The use of
NSAIDs in the investigated pain models was not able
to totally abolish the need for rescue analgesia, usually
IV-administered opioids. Taking into account that
most of the trials were performed with major abdom-
inal or orthopedic surgery patients, this could be ex-
pected. In this case, the use of surrogate outcomes

<table>
<thead>
<tr>
<th>Timing</th>
<th>Dose (mg)</th>
<th>Parecoxib-/ketorolac-treated patients (n)</th>
<th>Relative risk of a “good/excellent” evaluation with treatment versus ketorolac</th>
<th>NNH</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>20</td>
<td>183/133</td>
<td>0.85 (0.75–0.97)</td>
<td>NNH</td>
<td>18, 23, 24</td>
</tr>
<tr>
<td>Treatment</td>
<td>40</td>
<td>181/133</td>
<td>1.03 (0.89–1.18)</td>
<td></td>
<td>18, 23, 24</td>
</tr>
</tbody>
</table>

Results are given separately for 20 vs 40 mg. Ninety-five percent confidence intervals are given in parentheses. A number needed to harm (NNH) is presented only if there was a significant difference compared with the control group.

Table 4. Pooled Results of Randomized Controlled Trials of Injected Parecoxib Versus 30–60 mg of Injected Ketorolac on the Patients’ Global Evaluation of Study Medication

© International Anesthesia Research Society. Unauthorized Use Prohibited.
such as opioid consumption is widespread. The underlying assumption is that by preventing the need for rescue analgesics, usually narcotics, patients experience fewer opioid-related side effects and thus feel better in the postoperative period. Because opioids have a unique safety profile and are easy to titrate according to individual need, this is a valid concept only if patients judge the quality of their balanced analgesic regimen better than the conventional one, relying, for instance, solely on morphine administered via a PCA device. Even the need for more rescue treatment per se does not necessarily reflect dissatisfaction with the regimen if the patients are able to control the situation by themselves.

Consequently, it seems worthwhile to let patients decide what they think about the pain management as a type of “true outcome.” This concept bears the risk that, from a theoretical point of view, it is conceivable

Table 5. Pooled Results of Reported Adverse Effects in the Analyzed Randomized Controlled Trials of Injected Parecoxib Versus Placebo or Active Comparisons

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose</th>
<th>Patients treated with parecoxib</th>
<th>Competitor</th>
<th>Relative risk of an adverse effect with treatment versus competitor</th>
<th>NNT</th>
<th>No. of included trials in the analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any observed adverse effects</td>
<td>All</td>
<td>1106 Placebo</td>
<td>1.00 (0.95–1.05)</td>
<td>NNT 7.7 (5.9–11.1)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Any observed adverse effects</td>
<td>20 mg</td>
<td>427 Placebo</td>
<td>1.01 (0.91–1.12)</td>
<td>NNT 20 (11.1–50)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Any observed adverse effects</td>
<td>40 mg</td>
<td>679 Placebo</td>
<td>1.00 (0.95–1.06)</td>
<td>NNT 70 (59–111.1)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>All</td>
<td>773 Placebo</td>
<td>0.31 (0.21–0.46)</td>
<td>NNT 20 (11.1–50)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>All</td>
<td>1162 Placebo</td>
<td>0.96 (0.84–1.10)</td>
<td>NNT 20 (11.1–50)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>All</td>
<td>1160 Placebo</td>
<td>1.08 (0.82–1.42)</td>
<td>NNT 70 (59–111.1)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>All</td>
<td>889 Placebo</td>
<td>0.81 (0.61–1.08)</td>
<td>NNT 70 (59–111.1)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>All</td>
<td>532 Placebo</td>
<td>0.68 (0.48–0.97)</td>
<td>NNT 70 (59–111.1)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>All</td>
<td>604 Placebo</td>
<td>0.69 (0.35–1.33)</td>
<td>NNT 70 (59–111.1)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>All</td>
<td>473 Placebo</td>
<td>0.76 (0.49–1.20)</td>
<td>NNT 70 (59–111.1)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Abnormal breath sounds</td>
<td>All</td>
<td>388 Placebo</td>
<td>0.95 (0.64–1.14)</td>
<td>NNT 70 (59–111.1)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>All</td>
<td>532 Placebo</td>
<td>0.98 (0.64–1.49)</td>
<td>NNT 70 (59–111.1)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>All</td>
<td>443 Placebo</td>
<td>1.28 (0.58–2.80)</td>
<td>NNT 70 (59–111.1)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Postoperative anemia</td>
<td>All</td>
<td>263 Placebo</td>
<td>1.02 (0.55–1.88)</td>
<td>NNT 70 (59–111.1)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>All</td>
<td>443 Placebo</td>
<td>0.85 (0.14–5.04)</td>
<td>NNT 70 (59–111.1)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>All</td>
<td>396 Placebo</td>
<td>0.91 (0.51–1.61)</td>
<td>NNT 70 (59–111.1)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Any observed adverse effects</td>
<td>40 mg</td>
<td>80 Morphine</td>
<td>0.89 (0.73–1.10)</td>
<td>NNT 70 (59–111.1)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>All</td>
<td>162 Morphine</td>
<td>0.27 (0.12–0.62)</td>
<td>NNT 8.3 (5.6–20.0)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>All</td>
<td>162 Morphine</td>
<td>1.02 (0.73–1.42)</td>
<td>NNT 8.3 (5.6–20.0)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>All</td>
<td>162 Morphine</td>
<td>0.94 (0.58–1.53)</td>
<td>NNT 8.3 (5.6–20.0)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>All</td>
<td>162 Morphine</td>
<td>1.17 (0.62–2.21)</td>
<td>NNT 8.3 (5.6–20.0)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>All</td>
<td>162 Morphine</td>
<td>1.02 (0.13–7.91)</td>
<td>NNT 8.3 (5.6–20.0)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>All</td>
<td>162 Morphine</td>
<td>0.45 (0.28–1.82)</td>
<td>NNT 8.3 (5.6–20.0)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>All</td>
<td>162 Morphine</td>
<td>1.45 (0.26–7.26)</td>
<td>NNT 8.3 (5.6–20.0)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Any observed adverse effects</td>
<td>All</td>
<td>364 Ketorolac</td>
<td>0.93 (0.85–1.01)</td>
<td>NNT 8.3 (5.6–20.0)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Any observed adverse effects</td>
<td>20 mg</td>
<td>183 Ketorolac</td>
<td>0.95 (0.84–1.07)</td>
<td>NNT 8.3 (5.6–20.0)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Any observed adverse effects</td>
<td>40 mg</td>
<td>181 Ketorolac</td>
<td>0.90 (0.79–1.03)</td>
<td>NNT 8.3 (5.6–20.0)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>All</td>
<td>162 Ketorolac</td>
<td>0.15 (0.07–0.33)</td>
<td>NNT 4.2 (2.6–11.1)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>All</td>
<td>364 Ketorolac</td>
<td>0.97 (0.72–1.29)</td>
<td>NNT 4.2 (2.6–11.1)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>All</td>
<td>364 Ketorolac</td>
<td>0.83 (0.49–1.41)</td>
<td>NNT 4.2 (2.6–11.1)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>All</td>
<td>279 Ketorolac</td>
<td>1.31 (0.78–2.18)</td>
<td>NNT 4.2 (2.6–11.1)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>All</td>
<td>364 Ketorolac</td>
<td>0.71 (0.47–1.05)</td>
<td>NNT 4.2 (2.6–11.1)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>All</td>
<td>162 Ketorolac</td>
<td>0.60 (0.28–1.30)</td>
<td>NNT 4.2 (2.6–11.1)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>All</td>
<td>162 Ketorolac</td>
<td>0.58 (0.22–1.54)</td>
<td>NNT 4.2 (2.6–11.1)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>All</td>
<td>364 Ketorolac</td>
<td>1.59 (0.86–2.96)</td>
<td>NNT 4.2 (2.6–11.1)</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Ninety-five percent confidence intervals are given in parentheses. A number needed to treat (NNT) is presented only if there was a significant difference compared with the control group.
that satisfaction as judged by patients is not necessarily accompanied with real analgesic effects. One might argue that a drug that primarily enhances the patient’s mood would be judged superior to an effective but not mood- or vigilance-influencing drug. However, once the ability to relieve pain and not only to enhance the patient’s mood is established, it seems sensible to encourage such outcomes and to test whether our supposed achievements, in terms of pain relief and related outcomes (5), correlate with a real benefit in the patient’s view, as expressed by the patient’s global evaluation. Pain relief with parecoxib compared with placebo has been tested by using the total-pain-relief method and then obtaining an NNT with the calculated proportion of patients in each treatment group who achieved at least 50% of maximum possible pain relief (5). The investigation concerning whether improved patients’ global evaluation with parecoxib observed in single trials is robust, and, thus, to overcome the threat of random chance, is a typical area of application for meta-analyses because it has been shown that many patients are needed for credible estimates of the NNT or other related outcomes (19).

A popular and reliable tool for assessing a patient’s view is the four-point Likert scale (20). Such a scale is furthermore an appropriate means for use in analgesic trials because a satisfying correlation of a dichotomous end-point on a five-point Likert scale with actual observed pain relief has been demonstrated (21).

The fact that all trials consistently used the same scale for their assessment, thus keeping the variability between trials as small as possible, means that the patients’ global evaluation of study medication is an ideal dichotomous outcome when a separation between the proportion of patients being rather dissatisfied versus satisfied is performed. A good correlation between these patient-related subjective results and objective ones (for instance, at least 50% pain relief or remedication time) in previous analyses and the individual trials was reassuring and indicated that no irrelevant numbers were generated via this method.

Drug-Related Adverse Effects. One potential advantage of systematic reviews may lie in the detection of significant associations of adverse outcomes with certain interventions that occur less frequently than the investigated treatment effect. These adverse effects cannot be estimated with the requested level of certainty from single studies that are usually designed to accept or reject a null hypothesis of a more frequent treatment effect. Fortunately, this potential methodological strength was present in this analysis, although only nine valid trials were found, because reporting of adverse effects was good and the incidences of adverse outcomes were reported separately. However, even a systematic review of nine randomized trials may be underpowered to detect very rare effects. For this purpose, other methodological approaches and types of studies are needed when parecoxib is more widely used.

Safety issues in terms of unwarranted adverse effects were also one major reason that anesthesiologists were reluctant to perioperatively administer conventional NSAIDs. In the systematically reviewed trials on parecoxib, this is represented by the circumstance that head-to-head comparisons with an active analgesic (ketorolac) were performed only if the study drugs were first administered after surgery (treatment trials).

In contrast to long-term use in chronic pain patients, where gastrototoxicity plays a major role, acute effects on platelet aggregation and subsequent bleeding disorders limit perioperative use. For both of these adverse effects, the retrieved trials were not suited to provide adequate answers, because trial size and follow-up time were not suited; relevant outcomes, such as erosions and ulcers diagnosed via endoscopy, were not assessed; or bleeding was not monitored routinely and consequently throughout the trials. Furthermore, as described above, active comparisons were performed only in trials that focused on postoperative administration. Therefore, safety with respect to these questions must be extrapolated from other trials and analyses not performed in the perioperative setting (4,22). However, transferring these data to a single or short-term perioperative dose regimen seems dangerous and the relevance questionable.

The pooled data allow for a solid assumption that the perioperative use of parecoxib is not associated with increased overall adverse effects or with any of the single observed adverse effects compared with placebo. The relevance of sternal wound infections in cardiac surgery (16), a potential serious adverse effect, has yet to be determined. Interestingly, even though peripheral analgesics such as parecoxib have opioid-sparing effects, this did not result in any detectable difference in the incidence of nausea and vomiting between groups. However, parecoxib seems to be protective against fever and headache.

Data comparing morphine with parecoxib are sparse, so conclusions with respect to adverse effects should be drawn with caution. In comparison to injected ketorolac, data were sufficient to allow for an initial statement that there appeared to be no differences in minor complications between parecoxib (20 and 40 mg) and ketorolac (30–60 mg).

In conclusion, in the perioperative setting, injected parecoxib significantly improves patients’ global evaluation of the analgesic regimen compared with placebo. Parecoxib was judged better by means of dichotomous patients’ global assessment of the study drug if it was administered the first time as treatment instead of as prophylaxis. Parecoxib 40 mg seems to be more effective than 20 mg without being associated with
additional side effects. Both doses were equally well tolerated compared with placebo and in head-to-head comparisons versus morphine or ketorolac. Parecoxib 40 mg is equally effective compared to ketorolac 30–60 mg, from the patients’ point of view. Since intraoperative use might be safer compared with ketorolac and since a greater margin of safety can be obtained even with short-term use (22), parecoxib could become a valuable non-opioid analgesic for the perioperative period, if the IV route is necessary.

We thank Doris Denner, Pfizer GmbH, Karlsruhe (Germany), for responding to our inquiry.

References