Postoperative analgesia with parecoxib, acetaminophen, and the combination of both: a randomized, double-blind, placebo-controlled trial in patients undergoing thyroid surgery

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Background. We assessed the analgesic efficacy of parecoxib, acetaminophen, and the combination of both compared with placebo in patients undergoing elective thyroid or parathyroid surgery.

Methods. We randomized 140 patients to receive one of the following i.v. treatments using a double-blinded double-dummy technique: placebo, 80 mg 24 h⁻¹ parecoxib, 5 g 24 h⁻¹ acetaminophen, or 80 mg parecoxib plus 5 g acetaminophen. We provided rescue analgesia with piritramide delivered by a patient-controlled analgesia device. We measured opioid consumption and pain intensity over 24 h after operation.

Results. Patient characteristic data, anaesthetic, and surgical characteristics of the patients in the four groups were similar. Parecoxib, acetaminophen, and the combination significantly reduced opioid requirements during 24 h after surgery [mean (SD) 12.5 (10.9) mg for parecoxib, 14.2 (12.3) mg for acetaminophen, and 11.9 (10.7) mg for combination] compared with placebo [23.5 (15.3) mg, \(P<0.05\)]. However, the combination of parecoxib and acetaminophen did not have any advantage over individual drugs in terms of opioid consumption in our trial (\(P>0.05\)).

Conclusions. Parecoxib and acetaminophen effectively reduce postoperative opioid requirements after thyroid or parathyroid surgery. The combination of these drugs is not associated with a further reduction in opioid consumption.

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Parecoxib and acetaminophen are non-opioid analgesics with a well-documented efficacy after different surgical procedures. The use of non-opioid analgesics can reduce opioid-induced side-effects. Combining two non-opioid analgesics may increase the benefit, if an additive effect can be achieved.

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the enzymes cyclooxygenase (COX) -1 and -2. Only the inhibition of COX-2 is involved in analgesic, anti-inflammatory, and antipyretic effects of NSAIDs. The reduced activity of COX-1 is associated with adverse events of NSAIDs as gastrointestinal bleeding and platelet dysfunction. Selective COX-2 inhibitors—a subgroup of NSAIDs—act only at the isoenzyme COX-2 reducing COX-1 inhibition-related adverse events. Selective COX-2 inhibitors have reduced side-effects in the gastrointestinal system and on platelet function. We assumed that the combination of the selective COX-2 inhibitor parecoxib and acetaminophen may offer an effective way to treat postoperative pain and avoid adverse events.

Since the combination of acetaminophen and the selective COX-2 inhibitor parecoxib has not been investigated so far, we conducted a clinical trial investigating analgesic effects of acetaminophen, parecoxib, and their combination in patients undergoing strictly standardized thyroid or parathyroid surgery.
Methods

This prospective, randomized, double-blind placebo controlled trial was conducted at a university hospital in Germany, and it was approved by the local ethics committee.

Between December 2004 and May 2005, patients were enrolled in the study, if they were undergoing elective thyroid or parathyroid surgery, ASA I–III, aged between 18 and 80 yr, and they provided informed consent. Patients undergoing day-case surgery or thoracotomy were not eligible. Exclusion criteria were heart failure, liver failure, renal dysfunction, coagulopathy, severe bronchial asthma (i.e. previous hospital admission, long-term medication with bronchodilators and corticosteroids), or a history of adverse events after NSAIDs, acetaminophen, parecoxib, valdecoxib, celecoxib, or sulphonamides.

The day before surgery, the patients gave informed written consent to the study. Patients were introduced to the use of a patient-controlled analgesia (PCA) device and the documentation of postoperative pain or adverse effects on numerical analogue scales (NRS) or visual analogue scales (VAS).

Premedication, induction, and maintenance of general anaesthesia and also postoperative nausea and vomiting (PONV) prophylaxis were standardized in all participants. The patient’s regular oral medications were discontinued except for antihypertensive drugs.

We used midazolam 7.5 mg for premedication and dexamethasone 8 mg for PONV prophylaxis. We induced general anaesthesia with i.v. midazolam 1–2 mg, sufentanil 0.2–0.3 µg kg⁻¹ bodyweight up to 50 µg, and propofol 2–3 mg kg⁻¹. Tracheal intubation was facilitated with rocuronium 0.6 mg kg⁻¹. We maintained anaesthesia with desflurane 3–6 vol% and remifentanil 0.1–0.4 µg kg⁻¹ min⁻¹. In addition, all patients received dolasetron 12.5 mg at the end of surgery for PONV prophylaxis.

Patients were randomized to receive either placebo or one of the following: acetaminophen (Perfalgan®, Bristol-Myers Squibb, Germany), parecoxib (Dynastat®, Pfizer, Germany), or the combination of acetaminophen and parecoxib. The allocation sequence was obtained by a computerized randomization list. The allocation then was concealed using sealed numbered envelopes. For each new patient, the envelope with the smallest available number was broken after induction of general anaesthesia. A nurse, not involved in the perioperative care of the patient, opened the envelope and prepared the study medication outside the theatre. Patients and researchers were not aware of the study medication. Study medications were clear, colourless fluids avoiding visible differences between the study drugs.

About 30 min before the end of surgery, the patients received a bolus of the study drug I, that is, either placebo, acetaminophen, parecoxib or the combination of acetaminophen and parecoxib. After the bolus, we started an infusion over 24 h of the study drug II, that is, either acetaminophen (4 g 24 h⁻¹) or normal saline. Eight hours after surgery, the participants received a bolus of the study drug III, that is 40 mg parecoxib or normal saline (Table 1).

In the post-anaesthesia care unit, we provided all patients with a PCA pump via an i.v. line and allowed unlimited access while the patients were in the recovery room. The PCA device was a PEGA® plus [Venner Medical (Deutschland) GmbH, Kiel, Germany]. The PCA device delivered piritramide, an opioid used regularly in Germany. The potency ratio of piritramide/morphine equals 1/1.5. We used piritramide mainly because it is used in the majority of German hospitals.

Before discharge from the recovery room, the PCA pump was programmed as follows: no continuous infusion, bolus piritramide 2 mg, lock-out time 10 min, and maximum dose of piritramide in 4 h 20 mg.

We hypothesized that parecoxib, acetaminophen, or the combination of both result in a statistically significant reduction of postoperative opioid consumption in patients undergoing thyroid or parathyroid surgery.

The primary outcome of our study was the total opioid requirement over 24 h. We also determined the time until first postoperative opioid request. Secondary endpoints were the quality of pain control, overall patient satisfaction, and adverse events. Our patients documented pain intensity on an NRS from 0 (no pain) to 10 (worst pain) at 1, 8, and 24 h after surgery. The overall patients’ satisfaction was measured on a VAS from 0 (not at all) to 100 (very much satisfied). We interviewed the patients for adverse events the day after surgery. Patients were asked to report any adverse event, especially sedation, nausea, vomiting, shivering, or headache. The patient chart was reviewed for any hypertension, hypotension, or postoperative bleeding.

These data were obtained by a trained research assistant otherwise not involved in the study.

We calculated the sample size based on the assumption that an overall reduction in opioid consumption of about 30% (primary endpoint) would be a clinically important effect. In published studies, a reduction of 20–30% of

| Table 1 Study design |
| --- | --- | --- |
| 30 min before end of surgery | At the end of surgery | 8 h after surgery |
| Administration | Infusion over 15 min | Infusion over 24 h | Infusion over 15 min |
| Parecoxib | 40 mg parecoxib + 100 ml saline | 4 g acetaminophen | 40 mg parecoxib |
| Acetaminophen | 10 ml saline + 1 g acetaminophen | 4 g acetaminophen | 10 ml saline |
| Combination | 40 mg parecoxib + 10 ml saline | 40 mg parecoxib |
| Placebo | 10 ml saline + 100 ml saline | 500 ml saline | 10 ml saline |
opioid requirements was attributed to the use of COX-2 inhibitors\textsuperscript{5-7} or acetaminophen.\textsuperscript{8-9} Assuming a standard deviation (SD) of 0.66 of the expected difference, 35 patients per group provided a power of $>90\%$ to detect this difference using the Tukey–Kramer’s all-pair comparison with a type I error of $<5\%$.

Statistics

Data of piritramide consumption and pain intensities were treated as continuous. The results are given as mean (SD). Normal distribution of the data was confirmed using the Kolmogorow–Smirnow test. The analysis of continuous data was performed using the Tukey’s all pairs test. Qualitative data were tested with the $\chi^2$ test and in the case of statistical significance followed by Fisher’s exact tests as post hoc test without adjustments of the $P$-value. $P<0.05$ was considered statistically significant. To evaluate the supra- or infra-additivity of the two non-opioids, an exploratory analysis of variance (ANOVA) was planned. This was assumed when the interaction term of the two-way ANOVA was significant. We used the JMP 7 software (SAS institute Inc., Cary, NC, USA).

Results

A total of 140 patients were enrolled in this trial. Of these, 130 data sets were included in the final analysis. Ten patients were withdrawn because of major protocol violations (placebo, $n=1$; acetaminophen, $n=1$, parecoxib, $n=4$, parecoxib/acetaminophen, $n=1$), withdrawal of consent (placebo, $n=1$), and unplanned sternotomy (placebo, $n=1$; parecoxib/acetaminophen, $n=1$) (Fig. 1).

The four groups were comparable with respect to patient characteristics, duration of surgery, anaesthesia, and consumption of anaesthetics (Table 2). No statistically significant differences for duration of surgery, total remifentanil dose, or desflurane requirement were observed between the study groups. It may be important to note that all patients received remifentanil $10–20\ \mu g\ min^{-1}$, but no long-acting opioid at the end of surgery.

The overall piritramide request mean (SD) via PCA during 24 h after thyroid or parathyroid surgery was 23.5 (15.3) mg in the placebo group. Parecoxib and acetaminophen reduced the opioid requirement to 12.5 (10.9) and 14.2 (12.3) mg, respectively (Table 3, Fig. 2). However, the combination of both active drugs was not associated with a further decrease in opioid consumption [11.9 (10.7) mg]. An exploratory two-factorial ANOVA (MANOVA) indicated that the combination of both drugs exhibits an additional analgesic effect significantly less than what would be expected from a simple additive effect ($P=0.048$). Table 4 shows the data of statistical significance between the study groups.

The treatment groups had similar or less pain intensity than the placebo group at all time points. Placebo patients documented postoperative pain on an NRS scale of 4.6 (1.4), 2.3 (1.9), and 1.9 (1.8) at 1, 8, and 24 h, respectively, after surgery. One hour after surgery, patients in the placebo group documented the same pain intensity as those in the treatment groups (Table 3). Eight and 24 h after surgery, patients with parecoxib but not acetaminophen reported significantly reduced pain compared with placebo; parecoxib patients with and without acetaminophen reported significantly less pain than those in the acetaminophen group (Tables 3 and 4).

![Fig 1 Participant flow.](https://academic.oup.com/bja/article-abstract/104/6/761/232723)
The time until first opioid request was 28.1 (31.2) min in the placebo group. Parecoxib and acetaminophen significantly prolonged the time until first additional opioid requirement to 43.5 (78.9) and 45.3 (76.6) min, respectively ($P < 0.05$). Patients with the combination of both active drugs showed a trend to request opioids later than those with a single analgesic [60.0 (103.3) min, $P > 0.05$].

The overall satisfaction with anaesthesia management on a VAS (0–100) was 89.2 (17.9) in the placebo group with no significant difference compared with other groups (Table 3).

We observed adverse events during 24 h after surgery (Table 5). In the placebo group, 53.1% reported sedation, 25.0% nausea, 6.3% vomiting, 21.9% shivering, and 6.3% dysphagia after surgery. An elevated arterial pressure was documented in the charts of 9.4% of placebo patients. With the only exception of a significantly reduced incidence of nausea in the combination group, there were no statistically significant differences between the placebo and treatment groups ($P > 0.05$) (Table 5).

In two patients, postoperative bleeding complicated recovery. One of these patients (parecoxib group) was treated conservatively, and the other patient (acetaminophen group) required reoperation. No other serious adverse event was observed during the trial period.

**Discussion**

The reduction of opioid requirements using perioperative non-opioid analgesics in patients after surgery is important in reducing sedation, impaired pulmonary function, and constipation. We investigated the influence of parecoxib, acetaminophen, and their combination on postoperative piritramide consumption in a randomized, double-blind, controlled trial. Patients included in this analysis underwent thyroid or parathyroid surgery under general anaesthesia using standardized anaesthetic technique.
Parecoxib, acetaminophen, and postoperative pain

Parecoxib, acetaminophen, and their combination reduced postoperative opioid requirement significantly by 50%. However, the combination of parecoxib and acetaminophen was not superior to each substance alone, indicating that the combination of parecoxib and acetaminophen after thyroid or parathyroid surgery does not result in additive efficacy.

A secondary outcome variable of this trial was pain intensity after surgery. Eight and 24 h after surgery parecoxib, but not acetaminophen, was associated with significantly reduced pain scores compared with placebo, suggesting that parecoxib provides superior analgesia compared with placebo and acetaminophen.

The analysed number of patients in this trial allows the detection of clinically important differences. However, small differences between the study groups may go undetected.

Our patients received a remifentanil-based anaesthesia. However, the use of remifentanil can be associated with the development of an opioid-induced hyperalgesia. At the end of a remifentanil infusion, patients may have increased opioid requirements due to opioid-induced increased pain sensitivity. Therefore, the initial requirement of opioids may not only be related to the intraoperative trauma, but also reflect a remifentanil-associated hyperalgesia. Since all our patients underwent the same standards of remifentanil infusion, this may not have influenced differences between the study groups.

In a prospective randomized trial, acetaminophen and parecoxib were combined with dexamethasone or placebo. Dexamethasone decreased the need for opioids in the post-anaesthesia care unit to a similar degree in patients receiving acetaminophen or parecoxib. Therefore, the addition of dexamethasone may be a confounding factor in trials investigating the efficacy of non-opioid analgesia. However, in our study, all patients received the same dose of dexamethasone for PONV prophylaxis. Thus, an uncontrolled influence of dexamethasone seems to be unlikely.

The analgesic effects of parecoxib have been evaluated in numerous clinical trials. Only in one trial, the authors did not find a significant clinical analgesic effect of 40 mg parecoxib after laparoscopic cholecystectomy. After inguinal hernia repair, parecoxib reduced pain at rest significantly better than propacetamol, a prodrug of acetaminophen. We observed a similar small difference that may not be clinically important. In a cost analysis, parecoxib provided higher costs and greater patient satisfaction than acetaminophen. In other studies, no significant difference was described between parecoxib and acetaminophen.

Several randomized controlled trials showed a reduction in postoperative opioid consumption after parecoxib in laparoscopic cholecystectomy, total hip or knee arthroplasty, and hysterectomy. Our study confirms the notion of a significant opioid-sparing effect of parecoxib in postoperative pain management after thyroid surgery. Studies investigating the analgesic effects of combined parecoxib and acetaminophen have not been published so far.

Table 4 Statistical significance of the results. Significant difference was calculated for opioid consumption in treatment groups vs placebo. Within the treatment groups, we found significantly reduced pain intensity with the combination of parecoxib and acetaminophen vs acetaminophen alone

<table>
<thead>
<tr>
<th></th>
<th>Parecoxib vs placebo</th>
<th>Acetaminophen vs placebo</th>
<th>Parecoxib + acetaminophen vs placebo</th>
<th>Parecoxib + acetaminophen vs parecoxib</th>
<th>Parecoxib + acetaminophen vs acetaminophen</th>
<th>Parecoxib vs acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postop. 0.0011</td>
<td>0.0085</td>
<td>0.0009</td>
<td>0.9765</td>
<td>0.4415</td>
<td>0.4668</td>
<td></td>
</tr>
<tr>
<td>Pain 8 h postop.</td>
<td>0.0022</td>
<td>0.031</td>
<td>0.0013</td>
<td>0.76</td>
<td>0.528</td>
<td>0.787</td>
</tr>
<tr>
<td>Pain 24 h postop.</td>
<td>0.1201</td>
<td>0.0902</td>
<td>0.2211</td>
<td>0.7218</td>
<td>0.6375</td>
<td>0.9162</td>
</tr>
<tr>
<td>Pain at PACU</td>
<td>0.1646</td>
<td>0.1168</td>
<td>0.2744</td>
<td>0.75</td>
<td>0.6343</td>
<td>0.8829</td>
</tr>
<tr>
<td>Pain 8 h postop.</td>
<td>0.0059</td>
<td>0.845</td>
<td>0.0115</td>
<td>0.7802</td>
<td>0.0167</td>
<td>0.0086</td>
</tr>
<tr>
<td>Pain 24 h postop.</td>
<td>0.004</td>
<td>0.3534</td>
<td>0.0078</td>
<td>0.7892</td>
<td>0.072</td>
<td>0.0419</td>
</tr>
</tbody>
</table>

Table 5 Side-effects. Results are given as number (%) of patients reporting a side-effect. *P<0.05 vs parecoxib, acetaminophen, and placebo

<table>
<thead>
<tr>
<th></th>
<th>Parecoxib (n=31)</th>
<th>Acetaminophen (n=34)</th>
<th>Parecoxib + acetaminophen (n=33)</th>
<th>Placebo (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>15 (48.4)</td>
<td>16 (47.1)</td>
<td>12 (36.4)</td>
<td>17 (53.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (38.7)</td>
<td>10 (29.4)</td>
<td>2 (6.1)*</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (3.2)</td>
<td>2 (5.9)</td>
<td>1 (3.0)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Shivering</td>
<td>4 (12.9)</td>
<td>2 (5.9)</td>
<td>3 (9.1)</td>
<td>7 (21.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (12.9)</td>
<td>2 (5.9)</td>
<td>5 (15.2)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (6.5)</td>
<td>3 (8.8)</td>
<td>4 (12.1)</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Orthostatic dysregulation</td>
<td>0 (0.0)</td>
<td>3 (8.8)</td>
<td>1 (3.0)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2 (6.5)</td>
<td>0 (0.0)</td>
<td>2 (6.1)</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>1 (3.2)</td>
<td>1 (2.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
Several studies compared the analgesic efficacy of i.v. acetaminophen with other non-opioid analgesics. No significant differences were described, when acetaminophen was compared with diclofenac after tonsillectomy or orthopaedic surgery and with metamizole after breast or retinal surgery. However, there are trials confirming a superior analgesic efficacy of NSAIDs in non-dental surgery. Thus, the analgesic effects seem to be equal to or smaller than with other non-opioids. In our study, parecoxib was associated with better pain reduction than acetaminophen, but we did not find a statistically significant difference in opioid requirements.

Acetaminophen in combination with classical NSAID was analysed in several clinical trials. In gynaecologic surgery, the combination of acetaminophen with diclofenac reduced postoperative morphine consumption significantly more than acetaminophen alone. After tonsillectomy in children, the combination of ibuprofen with acetaminophen was associated with a significantly better reduction in postoperative opioid requests than the combination of the selective COX-2 inhibitor rofecoxib in combination with acetaminophen. These findings are consistent with published data in other non-dental surgeries and with the results of our study. An additive analgesic effect of acetaminophen has been described with NSAIDs, but not with selective COX-2 inhibitors, that is, parecoxib.

Classical NSAIDs accumulate in inflamed tissues better than acetaminophen. Moreover, parecoxib has been shown to rapidly reach the central nervous system and reduce central hyperalgesia. Since the reduction of central hyperalgesia is equal for parecoxib and acetaminophen, the lack of additional pain reduction of the combination of parecoxib and acetaminophen may be explained by the achievement of central and peripheral analgesia by parecoxib alone. It remains unclear why parecoxib exerts a peripheral and a central analgesic effect, but does not reduce perioperative piritramide consumption more than acetaminophen.

In a study of analgesic effects of acetaminophen and the combination with codeine, Bjune and colleagues showed the importance of postoperative pain intensity in studies evaluating analgesic efficacy. Patients with moderate baseline pain (VAS 40–60 mm) did not have analgesic efficacy of any tested drug, whereas patients with strong baseline pain (VAS>60) had significant analgesic effects of either drug. Since the pain intensity of our patients always was moderate, the assay sensitivity of analgesia in our trial may be lower than expected. The setting was obviously sensitive enough to detect differences between treatment and placebo. Nevertheless, the thyroid surgery setting may not be associated with an intensity of nociceptive stimulation necessary to detect a statistically significant reduction in opioid consumption of parecoxib compared with acetaminophen.

Although patients receiving a combination of parecoxib and acetaminophen reported a statistically significant reduction in nausea, we did not observe a difference in other adverse events in patients with parecoxib, acetaminophen, or the combination of both. Since the case number was not calculated for a detection of differences in the incidence of side-effects, we cannot draw specific conclusions from this observation. Beyond well-known contraindications, it is important to note that parecoxib is contraindicated in coronary artery bypass surgery. Acetaminophen should be avoided in patients with pre-existing liver dysfunction.

Parecoxib and acetaminophen both effectively reduce postoperative opioid requirements after thyroid and parathyroid surgery. The combination of the drugs did not result in an additive analgesic effect in this kind of surgery. The data of our study do not support the combination of parecoxib and acetaminophen for postoperative analgesia after thyroid surgery.

Conflict of interest

H.W. has received payments from Pfizer GmbH and Bristol-Myers Squibb for lectures.

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