

# Is the prophylactic use of non-opioids for post-operative analgesia always indicated? A randomized controlled trial in breast surgery

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## Abstract

**Aim:** To assess the analgesic efficacy of prophylactic parecoxib/valdecoxib, paracetamol or the combination of both compared to placebo in patients undergoing elective breast surgery.

**Methods:** We conducted a randomized double-blind clinical trial. We measured opioid consumption over 24 hours post-operatively.

**Results:** After breast surgery, patients in the placebo group required

very low amounts of additional piritramide ( $d_{\text{placebo}} = 3.51 \text{ mg} + 6.34 \text{ mg}$ ). The preventive use of parecoxib/valdecoxib, paracetamol, or the combination did not significantly reduce opioid requirements ( $p > 0.05$ ).

**Conclusion:** The prophylactic use of non-opioids is not generally recommended, because patients may not require specific post-operative analgesia at all.

**Keywords:** Parecoxib; Paracetamol; Valdecoxib; Post-operative pain.

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## Introduction

In the search for increased patient satisfaction with peri-operative pain management, the prevention of pain has evolved as a field of major clinical interest especially in ambulatory surgery. Several trials describe the successful prophylactic use of non-opioid analgesics for post-operative pain reduction, i.e. ketorolac, lornoxicam or tenoxicam [1–6]. More recently, similar prophylactic analgesic effects have been described for coxibs [7,8]. Even parecoxib and paracetamol pre-operatively may prevent post-operative pain [9,10].

To optimize prophylactic non-opioid analgesia, we conducted a prospective, randomized, double blind, clinical trial comparing the analgesic effects of parecoxib/valdecoxib, paracetamol or their combination with placebo in patients after breast surgery. Since valdecoxib was withdrawn from the market in 2005, we left the publication of the results aside. However, in the light of growing literature recommending the prophylactic use of non-opioids we felt that the results of our study may be important for the clinical decision to use analgesics prophylactically.

Planning the trial, our intention was an improvement of non-opioid analgesia and a reduction of opioid induced sedation, PONV, constipation and respiratory depression. Combining two non-opioid analgesics was supposed to increase the benefit, if an additive effect could be achieved [11]. Since non-opioid analgesics were not associated with a risk of respiratory depression, we applied them as basic analgesia, i.e. at a fixed regimen irrespective of pain complaints.

We investigated the analgesic efficacy of a coxib and paracetamol alone and combined. The combination of a non-steroidal antiinflammatory drug (NSAID/ Coxib) with paracetamol was chosen, because different sites of action might result in additive effects. In an autoradiographic investigation, Brune et al. found paracetamol in a lower concentration in inflamed tissues than classical non-steroidal antiinflammatory drugs (NSAID) [12]. Thus, paracetamol was supposed to have central effects, whereas NSAIDs

were considered to act in inflamed tissues. Since the distribution of cyclooxygenase-inhibitors differs substantially, additive analgesic effects of the combination of an NSAID and paracetamol may be expected. However, a systematic review of controlled clinical trials did not prove an additive analgesic effect of paracetamol and NSAIDs [13]. Therefore, we looked for a new way of combining non-opioids.

NSAIDs inhibit the enzymes cyclooxygenase –I and II. Only the inhibition of cyclooxygenase-II is involved in analgesic, anti-inflammatory and antipyretic effects of NSAIDs. The reduced activity of cyclooxygenase-I is associated with adverse events from NSAIDs - gastrointestinal bleeding and platelet dysfunction. Selective cyclooxygenase-II-inhibitors – a subgroup of NSAIDs - act only at the isoenzyme cyclooxygenase-II reducing cyclooxygenase-I-inhibition related adverse events. Selective cyclooxygenase-II-inhibitors are associated with decreased gastrointestinal side effects and no inhibition of platelet function. Parecoxib is a specific cyclooxygenase-II-inhibitor acting as a prodrug of valdecoxib. We assumed, that the combination of the selective cyclooxygenase-II-inhibitor parecoxib/valdecoxib and paracetamol may offer an effective way to treat post-operative pain and avoid adverse events.

Since the combination of paracetamol and the selective cyclooxygenase-II-inhibitor parecoxib/valdecoxib had not been investigated for prophylactic pain management before, we conducted a clinical trial investigating analgesic effects of a coxib, paracetamol, and their combination in patients undergoing breast surgery.

## Methods

This prospective, randomized, double blind trial was conducted at a university hospital in Germany, and it was approved by the local ethics committee. All included patients gave written and informed consent.

## Participants

Patients were enrolled in the study, if they were scheduled for elective

breast surgery, if they were aged between 18 and 80 years and in good health (American-Society-of-Anesthesiologists-classification ASA < 3).

We excluded patients with heart failure, liver failure or renal dysfunction, coagulopathy or a history of adverse events after NSAID, paracetamol, parecoxib, valdecoxib, celecoxib or sulfonamides. Patients with severe bronchial asthma, i.e. after previous hospital administration, long-term medication with bronchodilators and corticosteroids were not eligible for this trial. Subjects under current NSAID intake ten days before surgery were not eligible. We precluded subjects who refused to consent.

### Interventions

The day before surgery, all included patients were informed and gave written consent to the study. Patients were introduced to the documentation of post-operative pain or adverse effects on numerical analogue scales (NRS) or visual analogue scales VAS.

Premedication, induction and maintenance of general anaesthesia as well as PONV prophylaxis were standardized in all participants.

Oral standard medications were discontinued except for antihypertensive drugs.

We used 7.5 mg midazolam mg for premedication and induced general anaesthesia with 0.1 to 0.25 mg Fentanyl and 1-3 mg/kg bodyweight (BW) Propofol. The intubation of the trachea was facilitated with 0.25 mg/kg BW mivacurium. We maintained anaesthesia with 3-8 mg/kg BW/h Propofol as required. Routine antiemetic prophylaxis using 8 mg dexamethasone and 12.5 mg dolasetron were administered after induction of anaesthesia.

### Study medication

Thirty minutes before the end of surgery, our patients received an infusion of one of the study medications i.e. either parecoxib, paracetamol, the combination of parecoxib and paracetamol or placebo (Table 1). After recovery from anaesthesia, the study medication was continued with oral tablets. Patients received 6h, 12h, and 18 h after surgery two tablets with either 20 mg valdecoxib, 1000 mg paracetamol, or placebo (Table 1).

### Escape medication

If patients asked for additional analgesia, they received 3.75 mg piritramide intravenously.

### Objectives

We hypothesized, that parecoxib/ valdecoxib, paracetamol and the combination of both result in a statistically significant reduction of post-operative opioid consumption in patients undergoing breast surgery.

### Outcomes

The primary objective of our study was the reduction of opioid requirements over 24 hours. We documented the cumulative piritramide consumption over 24 hours after operation.

Secondary endpoints were adverse events. Our patients documented pain intensity on a numerical analogue scale NRS from 0 (=no pain) to 100 (= worst pain). Overall patient satisfaction was measured on a visual analogue scale VAS from 0 (=not at all) to 100 (=very much satisfied). We interviewed our patients for adverse events the day after surgery and counted the number of patients who reported a side effect.

Post-operatively, a trained research assistant otherwise not involved in the study evaluated piritramide consumption, pain and adverse events.

### Sample size

We calculated the sample size based on the assumption, that an overall reduction in opioid consumption of about 30 percent (primary endpoint), shown in other studies evaluating the opioid sparing effects of COX-2 inhibitors [14–17] or paracetamol [18–22] would be a clinically important effect. Assuming a standard deviation of 2/3 of the expected difference, 35 patients per group provide a power of 84% to detect this difference using the Tukey-Kramer's all-pair comparison with a type I error of less than 5%.

### Randomization

Patients were randomized to receive either placebo or one of the following active comparators: parecoxib/ valdecoxib, paracetamol, or the combination of coxib and paracetamol.

The allocation sequence was obtained by a computed random list. The result of this randomization process was concealed using sealed numbered envelopes. For each new patient the envelope with the smallest available number was broken after general anaesthesia had been induced. A nurse, not involved in the perioperative care of the patient, opened the envelope and prepared the study medication outside the theatre.

**Table 1** Study design.

	30 Min before end of surgery	6h post op	12 h post op	18 h post op
<b>Study group</b>	Infusion over 15 minutes	2 Tablets	2 Tablets	2 Tablets
<b>Parecoxib/ Valdecoxib</b>	40 mg Parecoxib + 100 ml saline	20 mg Valdecoxib + Placebo p.o.	20 mg Valdecoxib + Placebo p.o.	20 mg Valdecoxib + Placebo p.o.
<b>Paracetamol</b>	100 ml saline + 1g Paracetamol	Placebo + 1g Paracetamol	Placebo + 1g Paracetamol	Placebo + 1g Paracetamol
<b>Combination</b>	40 mg Parecoxib + 1g Paracetamol	20 mg Valdecoxib + 1g Paracetamol	20 mg Valdecoxib + 1g Paracetamol	20 mg Valdecoxib + 1g Paracetamol
<b>Placebo</b>	100 ml saline + 100 ml Saline	Placebo + Placebo	Placebo + Placebo	Placebo + Placebo

## Blinding

Patients and researchers were not aware of the study medication. Study medications were clear, colourless fluids and white tablets of identical shape avoiding visible differences between the study drugs.

## Statistics

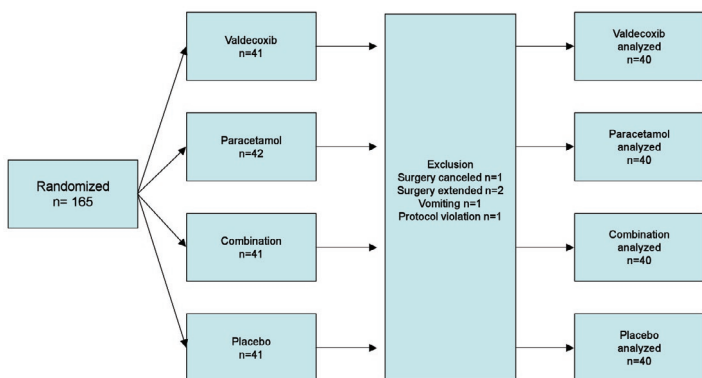
Data of piritramide consumption and pain intensities were treated as continuous data. The results are given as median (25th and 75th percentile) or mean (+ standard deviation). The analysis of the data was performed using the Tukey's all pairs test, the Wilcoxon U-test, and  $\chi^2$ -test where appropriate. P-values of  $p < 0.05$  were considered statistically significant.

## Results

### Participant flow

A total of 182 patients were eligible for our study and recruited from October 2003 to May 2004. Seventeen women met exclusion criteria and were not enrolled. 165 patients were included in this trial. Five patients were withdrawn because of cancelled surgery ( $n=1$ ), unexpected extension of surgery ( $n=2$ ), severe vomiting in the PACU ( $n=1$ ) followed by refusal of the patient to continue the trial, and major study violation ( $n=1$ ). Therefore, 160 data sets could be included in the final analysis (Fig. 1)

Figure 1 Participant workflow.



### Baseline data

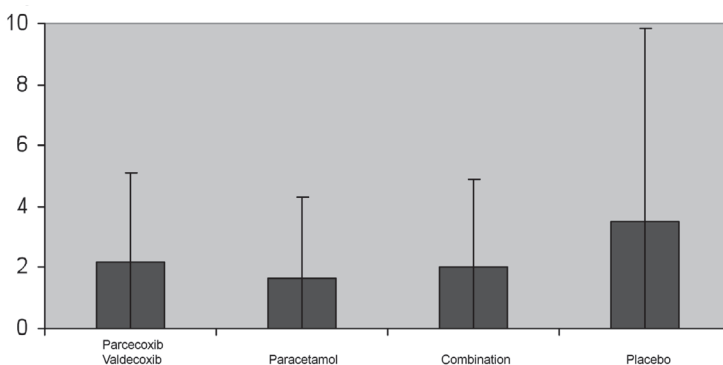
The four groups were comparable with respect to demographic data, kind of surgery and anaesthesia (Table 2). No statistically significant differences for total remifentanyl dose or desflurane-requirement were observed between study groups.

### Outcomes

The overall piritramide request (mean + SD) during the 24 hours after breast surgery was very low with 3.51 mg + 6.34 mg in the placebo group. Coxibs and paracetamol reduced the opioid requirement to 2.2 + 2.92 and 1.65 mg + 2.67 mg respectively (Table 3). However, the differences between placebo and treated groups were not statistically significant (Fig. 2). The combination of both active drugs was not associated with a further decrease of opioid consumption (2.0 mg + 2.91 mg).

The performance of the study was not associated with increased pain intensity in any study group supporting the notion of post-operative pain management as being equally sufficient over all study groups. Placebo patients documented post-operative pain intensity one and 24 hours after surgery on a NRS<sub>placebo</sub> 1h = 2.83 ± 2.0, and NRS<sub>placebo</sub> 24h = 1.69 ± 4.29. One and twenty-four hours after surgery, patients with a coxib (parecoxib/ valdecoxib), paracetamol or the combination of both did not report significantly reduced pain compared to placebo (Table 3).

Figure 2 Piritramide consumption (mg/24h).



Data are given as mean and standard deviation.

The average time until first opioid request was 62.4 + 43.5 min in the placebo group. Paracetamol but not valdecoxib or the combination prolonged the time until first additional opioid requirement to 93.5 + 129.0 min ( $p < 0.05$ ), 63.6 + 90.4 min and 36.5 + 14.3 min (Table 2).

### Side effects

We documented adverse events during the 24 hours after surgery (Table 4). In the placebo group, no patient reported pruritus, 20 % nausea or vomiting, 5 % shivering, 0 % elevated blood pressure or palpitation, 2.5 % hypotension and 10 % headache after surgery. No significant differences were observed between placebo and treated groups (Table 4).

Bleeding occurred in 5% of placebo patients, in no coxib-treated patient, one paracetamol and three participants in the combination group. No other serious adverse event was observed during the trial period.

## Discussion

The reduction of opioid requirements in patients after surgery is an important intention of peri-operative non opioid analgesic use reducing sedation, impaired pulmonary function, PONV and constipation. We investigated the influence of prophylactic parecoxib/ valdecoxib, paracetamol and their combination on post-operative piritramide consumption in a randomized double blind placebo-controlled trial. Patients included in this analysis underwent elective breast surgery under general anaesthesia.

Placebo patients reported very low pain intensity and required almost no opioid analgesics after breast surgery. Therefore, the prophylactic use of non-opioids was not always necessary in the investigated group of patients. Parecoxib/ valdecoxib, paracetamol and their combination did not reduce post-operative opioid requirement significantly. The secondary outcome parameter of this trial was pain intensity after surgery. One and twenty-four hours after surgery we did not find a significant difference in pain intensity between placebo and treated groups.

It is an important issue to note that the preventive use of analgesics requires not only a favourable ratio of efficacy and risks, but also should be based on the proof of a pain intensity justifying the therapy.

In a study of the analgesic effects of paracetamol and the combination with codeine, Bjune at al. showed the importance of post-operative pain intensity in studies evaluating analgesic efficacy [23]. Patients with moderate baseline pain (VAS 40 to 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 very low, the assay-sensitivity of analgesia in our trial is obviously lower than

**Table 2** Baseline data.

	Parecoxib/ Valdecoxib (n = 40)	Paracetamol (n = 40)	Combination (n = 40)	Placebo (n = 40)
<b>Age (years), median</b>	47 (38; 62)	53 (42; 62)	51 (43; 62)	54 (42; 62)
<b>Height (cm), median</b>	165 (163; 168)	165 (163; 168)	164 (162; 169)	164 (160; 168)
<b>Weight (kg), median</b>	68 (59; 78)	73 (63; 80)	65 (62; 74)	66 (60; 70)
<b>ASA I n (%)</b>	12 (30)	19 (47,5)	15 (37,5)	13 (32,5)
<b>ASA II, n (%)</b>	24 (60)	17 (42,5)	24 (60)	24 (60)
<b>ASA III, n (%)</b>	3 (7,5)	3 (7,5)	1 (2,5)	3 (7,5)
<b>ASA unknown, n (%)</b>	1 (2,5)	1 (2,5)	0 (0)	0 (0,0)
<b>Biopsy or lumpectomy n (%)</b>	35 (82,5)	33 (82,5)	33 (85)	31 (75,5)
<b>Plastic surgery, n (%)</b>	3 (7,5)	5 (12,5)	4 (10)	6 (15)
<b>Other breast surgery, n (%)</b>	2 (10)	2 (5)	2 (5)	3 (7,5)
<b>Duration of anesthesia (minutes), median</b>	104 (70; 138)	89 (60; 104)	85 (67; 106)	80 (67; 118)
<b>Overall Fentanyl dose (mg), median</b>	0.3 (0.2; 0.4)	0.25 (0.25; 0.4)	0.25 (0.2; 0.35)	0.25 (0.2; 0.4)
<b>Overall Remifentanyl dose (mg), median</b>	3.0 (2.6; 4.3)	3.0 (2.6; 4.3)	4.8 (1.8; 6.3)	5.33 (3.9; 6.6)
<b>Overall Propofol (mg), median</b>	700 (550; 950)	700 (512; 850)	650 (455; 800)	550 (500; 950)

Data of median are given with 25th and 75th percentile.

**Table 3** Results.

	Parecoxib/ Valdecoxib	Paracetamol	Combination	Placebo	p-value
<b>Piritramide 1 h post op (mg), mean (sd)</b>	1.81 (2.58)	0.9 (1.63)	1.75 (2.74)	1.21 (2.25)	n.s.
<b>Piritramide 24 h op (mg), mean (sd)</b>	2.2 (2.92)	1.65 (2.67)	2.0 (2.91)	3.51 (6.34)	n.s.
<b>First request of Piritramide (min), mean (sd)</b>	63.6 (90.4)	93.5 (129.0)	36.5 (14.3)	62.4 (43.5)	n.s.
<b>Number of opioid-free patients, n (%)</b>	33 (82.5)	34 (85)	32 (80)	23 (57.5)	n.s.
<b>Pain 1 h postoperative (VAS 0-100), mean (sd)</b>	2.68 (2.0)	2.73 (14.29)	2.58 (11.29)	2.83 (2.0)	n.s.
<b>Pain 24 h postoperative (VAS 0-100), mean (sd)</b>	1.0 (1.4)	1.54 (12.12)	0.98 (12.29)	1.69 (4.29)	n.s.

**Table 4** Side effects.

	Parecoxib/ Valdecoxib (n = 40)	Paracetamol (n = 40)	Combination (n = 40)	Placebo (n = 40)	p-value
Pruritus, n (%)	5 (12.5)	2 (5)	2 (5)	0 (0)	n.s.
Nausea/ vomiting, n (%)	7 (17.5)	10 (25)	5 (12.5)	8 (20)	n.s.
Shivering, n (%)	5 (12.5)	6 (15)	0 (0)	2 (5)	n.s.
Hypertension, n (%)	3 (7.5)	1 (2.5)	2 (5)	0 (0)	n.s.
Hypotension, n (%)	3 (7.5)	5 (12.5)	2 (5)	1 (2.5)	n.s.
Headache, n (%)	4 (10)	3 (7.5)	3 (7.5)	4 (10)	n.s.
Post-operative bleeding, n (%)	0 (0)	1 (2.5)	3 (7.5)	2 (5)	n.s.

expected. Therefore, our study setting was not associated with an intensity of nociceptive stimulation necessary to detect a statistically significant reduction of opioid use.

Classical non steroidal anti-inflammatory drugs accumulate in inflamed tissues better than paracetamol [12]. Moreover, parecoxib has been shown to rapidly reach the central nervous system and reduce central hyperalgesia [24,25]. In an experimental setting, the reduction of central hyperalgesia was equal for parecoxib and paracetamol [25]. Thus, the lack of additional pain reduction of the combination of parecoxib and paracetamol may be explained by the achievement of central and peripheral analgesia by parecoxib alone.

In our study, we did not observe a statistically significant reduction of the incidence of side effects. 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 [26]. Paracetamol should be avoided in patients with pre-existing liver dysfunction.

## Conclusion

The prophylactic use of parecoxib/ valdecoxib, paracetamol or the combination is not generally recommended after breast surgery, because the pain intensity after this kind of operation may not require analgesics. Therefore, non opioid analgesic should be applied as requested only.

The prophylactic use of analgesics requires not only a favourable ratio of efficacy and risks, but also should be based on the proof of a pain intensity justifying the therapy.

## Conflict of interest

HW received payments for lectures from Bristol Myers Squibb and Pfizer.

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