The Effects of Paracetamol and Parecoxib on Kidney Function in Elderly Patients Undergoing Orthopedic Surgery

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The common adverse effects of traditional nonsteroidal antiinflammatory drugs on renal function include reductions in renal blood flow, glomerular filtration rate, and sodium and potassium excretion, mainly via inhibition of renal cyclooxygenase. We designed the present study to determine the effects of IV paracetamol or parecoxib on renal function in elderly patients undergoing orthopedic surgery. Seventy-five patients (76 ± 8 yr, mean ± SD) undergoing hip replacement or surgery of the femoral shaft completed this randomized and placebo-controlled study. After their arrival in the postanesthesia care unit, patients received an initial dose of the study medication, paracetamol 1000 mg IV ($n = 25$), parecoxib 40 mg IV ($n = 25$), or saline IV ($n = 25$); subsequent doses were administered for the next 3 days. Opioids were provided as rescue medication. Blood and urine samples were collected before and after surgery, and markers of renal function were determined. During the first 2 h after the initial dose of parecoxib, creatinine clearance was slightly diminished (125 ± 83 to 86 ± 45 mL/min, $P < 0.05$), whereas no significant decrease of creatinine clearance was observed in the placebo and paracetamol groups. After all treatments, sodium and potassium excretion as well as urine albumin and α-1-microglobulin were transiently increased (group differences: not signicifant). In conclusion, glomerular and tubular functions were transiently affected in all patients after orthopedic surgery; however, the differences between the treatment groups were small and not clinically relevant. Further studies are warranted to determine adverse renal effects of longer-lasting therapy with these drugs, especially in patients with renal impairment or concomitant diseases.

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Pain control is important for elderly patients undergoing surgery. Opioid analgesics and conventional nonsteroidal antiinflammatory drugs (NSAIDs) dominate current treatment strategies for postoperative pain states. However, the administration of opioids is often limited by side effects in elderly patients, i.e., sedation, respiratory depression, constipation and/or paralytic ileus, and urinary retention. On the other hand, classic NSAIDs inhibit prostaglandin production by both cyclooxygenase (COX) isoenzymes, COX-1 and COX-2, producing adverse effects on the gastrointestinal tract, platelets, and kidney (1–3). As a result, the use of combinations of opioids and NSAIDs has been used in elderly patients as part of a multimodal strategy ("balanced analgesia") to enhance analgesia while reducing the dose-related side effects (4–6).

Recently, two injectable analgesics with an improved safety profile have been developed for postoperative pain therapy: paracetamol and parecoxib. Paracetamol (acetaminophen) is probably the most widely used analgesic worldwide. It has the advantage of an extremely good safety profile at therapeutic doses and it causes none of the side effects associated with opioids or NSAIDs (4). Parecoxib sodium is a parenterally administered inactive prodrug of the anti-inflammatory, selective COX-2 inhibitor, valdecoxib, which is more than 28,000 times more selective for COX-2 than it is for COX-1 (7). In contrast to nonselective NSAIDs, parecoxib has been shown to have only minor effects on gastrointestinal mucosa or platelet function (8,9).

However, there is unequivocal evidence that both COX isoenzymes are present in the kidney in constitutive and inducible forms, which suggests that selective COX-2 inhibitors might have the same effects on renal prostaglandins (PG) as traditional NSAIDs (3,10–12). Therefore, the aim of this study was to determine the effects of the two injectable analgesics, paracetamol and parecoxib, on renal function in patients at risk for adverse renal effects, i.e., elderly patients undergoing hip replacement or surgery of the femoral shaft.

Brief accounts of the present work have been published in abstract form (13).

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METHODS

After approval by the ethics committee of the Medical Faculty of the University of Erlangen, a prospective, randomized, double-blind and placebo-controlled study of elderly patients at least 65 yr old undergoing hip replacement or surgery of the femoral shaft was initiated. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki from December 2002 to December 2003 at the University Hospital Erlangen.

Patients were considered ineligible if they had angina or congestive heart failure, recent history of myocardial infarction, coronary angioplasty, coronary arterial bypass, stroke or transient ischemic attack, uncontrolled hypertension or uncontrolled diabetes mellitus, renal disease, bleeding disorders, or any disease that the investigator believed would pose a risk to the patient. Other exclusion criteria were allergy to NSAIDs, paracetamol, opioids or sulfonamids, or a history of significant clinical or laboratory abnormalities that contraindicated the use of paracetamol, parecoxib, or opioids. Furthermore, patients were not eligible if they had a recent history of analgesic or alcohol abuse, or required treatment with strong opioids or antidepressants. If a patient had received NSAIDs or COX-2 inhibitors, there was a washout period of at least 72 h and the weak opioid, tramadol, was provided as a substitute. The supplementary use of diuretics was prohibited during the observation period.

Patients were recruited the afternoon before surgery. After providing informed consent to take part in the study, they were instructed by an anesthesiologist on the use of the numerical rating scale (NRS), identifying 0 as "no pain" and 10 as "worst imaginable pain." Randomization of the study medication (parecoxib versus paracetamol versus saline) was performed by computer-generated codes maintained in sequentially numbered, opaque envelopes. Additional envelopes were provided if patients had to be excluded after recruitment and randomization.

All patients were premedicated with 3.75 mg oral midazolam 30–60 min before induction of anesthesia. Anesthesia was induced with 1–2 μg/kg of fentanyl and 0.2 mg/kg of etomidate, followed by 0.6 mg/kg of rocuronium to facilitate orotracheal intubation. After intubation, the patients' lungs were ventilated to normocapnia with sevoflurane in an air-oxygen mixture. A central venous catheter was placed via the superior vena cava and a urinary catheter was placed into the bladder of all patients.

With the exception of opioid administration, the maintenance of anesthesia was left to the discretion of each anesthesiologist. Every patient had to receive at least 4 μg/kg of fentanyl before surgical incision. The last dose of fentanyl had to be administered at least 30 min before the termination of the surgical procedure. The surgical procedures were performed by three general surgeons who often worked together, thus limiting surgical variation.

All patients were transferred to the postanesthesic care unit (PACU) for at least 6 h. Immediately after arrival, patients received a IV infusion of 1000 mg paracetamol (Perfalgan®, Bristol-Myers Squibb, Munich, Germany), 40 mg parecoxib (Dynastat®, Pfizer, Karlsruhe, Germany), or saline over 10 min. All study medication solutions were prepared by a hospital pharmacist who was not involved in the data collection. The anesthesiologist, the nursing staff, and the investigators were all blinded to the treatment. Subsequent doses of the same study medication were administered at 6-h (paracetamol) and 12-h (parecoxib) intervals for at least 3 days. At the surgical ward, patients and nursing staff were unblinded to the medication.

Venous blood samples were taken to determine serum Cystatin C, creatinine, blood urea nitrogen (BUN), and liver biochemistry (aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, international normalized ratio, and partial thromboplastin time). Additionally, urine samples were taken to evaluate creatinine clearance and urinary excretion of sodium, potassium, albumin, and α1-microglobulin. Samples were obtained immediately after insertion of the catheters, immediately after arrival at the PACU, and 2, 4, and 6 h after the first dose of the study medication. Serum creatinine at the end of every urine collection interval was used for calculating creatinine clearance. Furthermore, serum Cystatin C, creatinine, BUN, and liver biochemistry were obtained on the first, second, and third postoperative days.

For estimation of fluid balance, the central venous pressure (CVP) was determined immediately before surgery and immediately after arrival at the PACU.

Pain intensity was evaluated every 15 min. If pain intensity in rest exceeded 4 (of 10), 3 mg piritramide was administered by the nursing staff. Our experience with patient-controlled analgesia (PCA) in elderly patients indicated that they might have difficulties using PCA administration pumps in many cases. Therefore, a nurse-controlled analgesic regimen was chosen instead of PCA pumps. If a patient requested additional analgesia on the surgical ward, IV infusions of piritramide or tramadol were provided as rescue medication. Thus, two types of opioids were used in the study. For purpose of comparisons, morphine equianalgesic dosages (MED) were calculated, considering 1 mg of the MED equal to 1 mg piritramide (Dipidolor®, Grünenthal, Aachen, Germany), and to 10 mg tramadol (Tramal®, Grünenthal, Aachen, Germany) (14,15). Mean pain intensities were determined every 2 h until the first postoperative day and every 12 h until the end of the observation period.

The primary objective of the study was to detect treatment differences in creatinine clearance. The sample size was based on a study by Swan et al. (11), in

Table 1. Patient Numbers During the Study

Characteristics	Gender	Placebo	Paracetamol	Parecoxib
Randomized	Male	12	15	11
	Female	16	12	17
Adverse events	Male	0	1	0
	Female	0	0	0
Treatment failure	Male	0	0	0
	Female	1	0	0
Prohibited medication	Male	1	0	2
	Female	1	1	1
Completed study	Male	11	14	9
	Female	14	11	16

Values are numbers of patients. There were no significant differences among the groups.

which single doses of 250 mg or multiple doses of 12.5 or 25 mg rofecoxib were administered to elderly patient. They found a significant decrease in glomerular filtration rate (GFR) and creatinine clearance during the first 6 h after administration of the COX-2 inhibitor when compared with placebo. Based on these data, a sample size estimate indicated that 24 patients per group would give a power of 80% at an α-level of 0.05 for detecting a difference in creatinine clearance of at least 20% between the treatments. The study size was thus prospectively set to 75 patients, with 25 patients in each group.

Age, weight, height, duration of surgery and anesthesia, and cumulative MEDs were compared by one way analysis of variance (ANOVA). The distribution of gender, incidences of preexisting diseases, and ASA status were analyzed using Fisher's exact test. Kidney function, liver biochemistry, MEDs, and pain ratings over the time were statistically evaluated using repeated measures, ANOVA. Differences at individual time points were compared using planned comparisons, corrected with the Bonferroni procedure. Correlations were calculated using the Spearman R coefficient. Significance levels throughout this study were $P < 0.05$; all data are presented as mean ± SD, except for figures, in which data are displayed as mean ± 95% confidence interval (CI). The STATISTICA software package (Statsoft, Tulsa, NC) was used for statistical analyses.

RESULTS

A total of 83 patients were randomly selected to receive placebo ($n = 28$), paracetamol ($n = 27$), or parecoxib ($n = 28$). Six patients were withdrawn from the study because of prohibited medication after surgery (NSAIDs, opioids other than piritramide or tramadol); one patient was excluded because of a treatment failure (parecoxib instead of placebo); and one patient was excluded because he developed urticaria at the PACU 4 h after the initial paracetamol infusion (Table 1). The patients were replaced according to the procedure described earlier.

Finally, 41 women and 34 men finished the study protocol. Their average age (±SD) was 76 ± 8 yr (range, 65–94 yr). All groups were comparable with regard to age, weight, height, distribution of sex, preexisting diseases, and ASA status (Table 2). Type and lengths of surgical and anesthetic procedures were similar, leading to a mean of about 152 (±38) min duration of anesthesia (Table 3). Furthermore, consumption of crystalloids and colloids were similar across the treatment groups, leading to a slight but insignificant decrease in CVP when compared with the initial value. No patient had to be excluded from the study because of a need for diuretics during the observation period. There was no perioperative mortality (<30 days) among the 75 patients enrolled in our study.

During the first 2 h after administration of the study medication, creatinine clearance was significantly diminished in the parecoxib group (−49.2 mL/min, $P < 0.05$) (Fig. 1A), whereas no significant reduction of the creatinine clearance was noticed in the paracetamol and placebo groups (−17.1 and −23.4 mL/min, not significant, respectively). Creatinine clearance recovered after 4 h (Fig. 1A). No positive correlation was found between the decrease in creatinine clearance and baseline values of serum creatinine, or creatinine clearance. Urinary excretion of sodium, potassium, and albumin α1-microglobulin were transiently increased, with no statistically significant differences between the treatment groups (Fig. 1B–E).

A significant correlation was observed between serum Cystatin C and creatinine clearance ($n = 225$, Spearman R, −0.36, $P < 0.001$). However, in contrast to creatinine clearance, no decrease in Cystatin C levels was observed immediately after administration of parecoxib (Fig. 2). Furthermore, no clinically significant differences in serum creatinine, BUN, or liver biochemistry were determined among the treatment groups.

The nurse-controlled analgesia led to an adequate analgesia in all groups. Pain intensities were not different across the groups, with mean NRS ratings of about two to three during the first postoperative day (Fig. 3). Thereafter, pain intensities decreased, reaching significantly reduced NRS ratings on the first postoperative day (parecoxib), on the second postoperative day (paracetamol), and on the third postoperative day (placebo).

During the observation period, patients in the paracetamol group tended to consume less MEDs than

Table 2. Demographic and Baseline Characteristics

Characteristics	Placebo ($n = 25$)	Paracetamol ($n = 25$)	Parecoxib ($n = 25$)
Age (yr)			
Mean (SD)	76.7 (8.6)	76.7 (8.9)	76.0 (8.0)
Range	66–94	65–92	65–90
Sex			
Male *n* (%)	11 (44)	14 (56)	9 (36)
Female *n* (%)	14 (56)	11 (44)	16 (64)
Height (cm)			
Mean (SD)	167.7 (9.0)	167.2 (8.1)	162.7 (8.1)
Range	155–186	153–189	150–178
Weight (kg)			
Mean (SD)	69.1 (13.5)	74.0 (14.7)	69.8 (12.2)
Range	47–96	55–127	45–100
Serum creatinine (mg/dL)			
Mean (SD)	0.85 (0.25)	0.87 (0.21)	0.85 (0.17)
Range	0.48–1.60	0.50–1.36	0.59–1.19
Preexisting diseases			
Coronary heart disease *n* (%)	4 (12)	6 (24)	5 (20)
Hypertension *n* (%)	13 (52)	15 (60)	11 (44)
Diabetes *n* (%)	3 (12)	4 (16)	3 (12)
ASA (*n*)			
I	2	4	4
II	6	7	6
III	17	14	15

There were no significant differences among the groups.

ASA: risk classification according to the American Society of Anesthesiologists.

Table 3. Surgical and Anesthetic Characteristics

Characteristics	Placebo ($n = 25$)	Paracetamol ($n = 25$)	Parecoxib ($n = 25$)
Type of surgery			
Hip replacement *n* (%)	17 (68)	20 (80)	19 (76)
Femoral shaft *n* (%)	8 (32)	5 (20)	6 (24)
Duration of surgery (min)			
Mean (SD)	118.8 (38.5)	121.2 (31.1)	112.8 (43.7)
Range	66–251	54–184	43–204
Duration of anesthesia (min)			
Mean (SD)	153.0 (39.0)	153.5 (33.6)	149.3 (41.3)
Range	105–273	72–221	78–230
Fluid requirements			
Cristalloids (L)			
Mean (SD)	3.0 (1.0)	2.8 (1.2)	2.7 (1.0)
Range	1.5–5.5	1.0–7.0	1.0–5.0
Colloids (L)			
Mean (SD)	0.4 (0.3)	0.6 (0.5)	0.4 (0.3)
Range	0–1.0	0–1.5	0–1.0
Central venous pressure before sugery (cm H_2O)			
Mean (SD)	13 (6)	14 (6)	14 (5)
Range	4–24	6–22	7–20
Central venous pressure after surgery (cm H_2O)			
Mean (SD)	11 (4)	13 (4)	12 (4)
Range	7–20	5–20	8–18

There were no significant differences among the groups.

patients receiving parecoxib or placebo ($P < 0.1$, by ANOVA) (Fig. 3). The reduction in MED consumption with paracetamol was significant during the first postoperative day when compared with the placebo group (38 ± 22 vs 17 ± 22; $P < 0.05$, by Bonferroni-corrected planned comparisons). However, patients and nursing staff were unblinded to the treatment at this time point; thus, a placebo effect cannot be excluded.

DISCUSSION

Non-opioids, such as NSAIDs, COX-2 inhibitors, and paracetamol, are widely used for the treatment of postoperative pain; however, these drugs may be associated with adverse renal effects (12). These effects are mainly caused by the inhibitory effects of both COX-isoforms on renal PG synthesis, especially PGE_2,

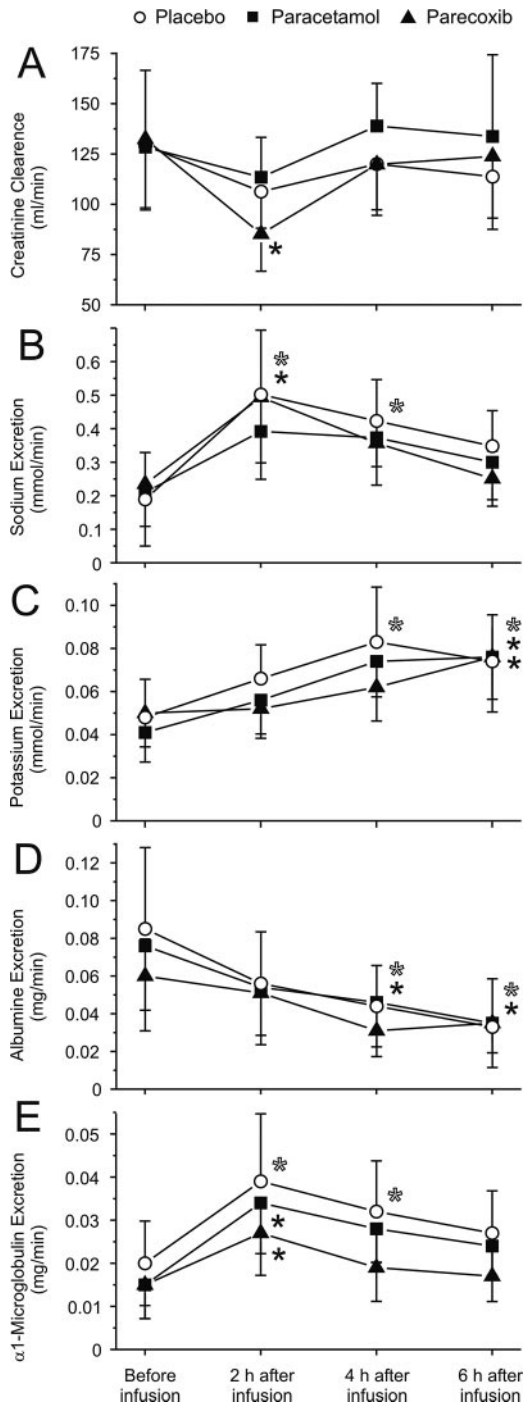

Figure 1. Creatinine clearance was significantly diminished in the parecoxib group during the first 2 h (A). Urinary excretion of sodium (B), potassium (C), albumin (D), and α1-microglobulin (E) were transiently increased, with no statistically significant differences between the treatment groups. Values are mean ± 95% CI, $*P < 0.05$ vs baseline, by ANOVA and Bonferroni-corrected *post hoc* comparisons.

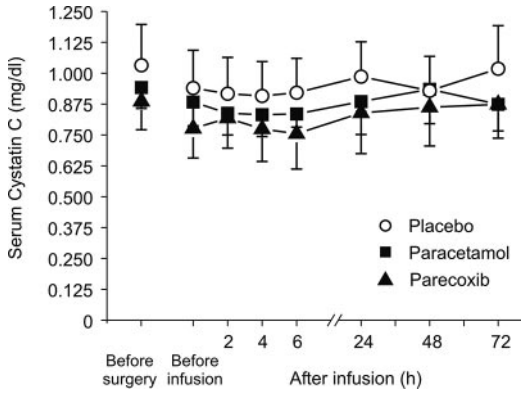

Figure 2. No significant differences were observed in serum Cystatin C across the treatment groups. Values are mean and 95% CI.

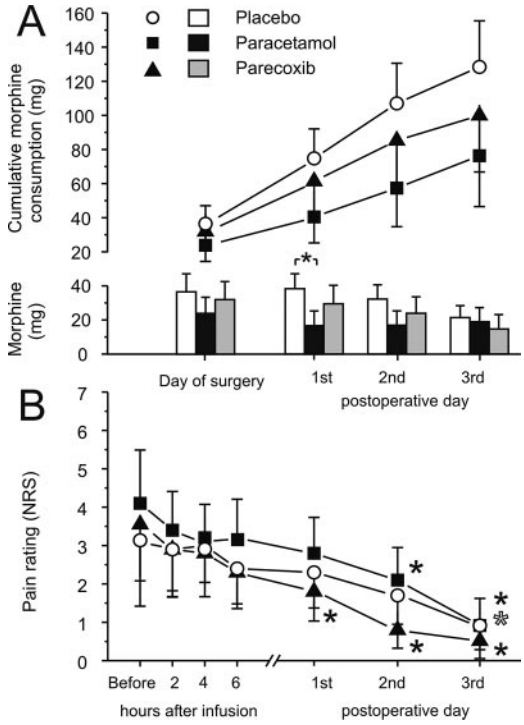

Figure 3. (A) Upper panel: the cumulative morphine equianalgesic dosages (MED) consumed over 72 h after surgery in patients taking paracetamol or parecoxib was slightly decreased when compared with placebo ($P < 0.1$, by ANOVA). Lower panel: morphine equianalgesic dosages (MED) during fixed time intervals in patients taking paracetamol, parecoxib, or placebo. Values are mean and 95% confidence interval, $*P < 0.05$, by ANOVA. (B) Pain ratings decreased significantly at the first postoperative day at the earliest. No differences were observed across the treatment groups. Values are mean and 95% CI, $*P < 0.05$ vs baseline, by ANOVA and Bonferroni-corrected *post hoc* comparisons.

PGI_2, and prostacyclin. PGE_2 decreases sodium reabsorption at the thick ascending loop of Henle, while PGI_2 stimulates renin release, which in turn increases aldosterone (12,16,17). Aldosterone increases sodium reabsorption and potassium secretion at the distal nephron. Prostacyclin is also a potent vasodilatator that maintains GFR and renal blood flow in patients with decreased actual or effective circulating volume (12,17).

Thus, inhibiting PGs can cause fluid and electrolyte disturbances and acute renal failure. However, these adverse effects tend to occur especially in patients who have concomitant diseases, e.g., in patients with acute or chronic renal failure, or those who have either actual or effective circulating volume depletion (18–20). Other risk factors include preexisting hypertension or diabetes. The majority of the population

observed in the present study had one or more of these concomitant diseases and was presumed to be at risk for the development of adverse renal effects. These adverse effects were further aggravated by the type of orthopedic surgery, which is often accompanied with acute changes of the actual or effective circulating volume.

Generally, COX-2 inhibitors and paracetamol are thought to have only minor effects on renal function, as they do not affect constitutively expressed COX-1. However, there is evidence that selective COX-2 inhibitors might have the same effects on renal PGs as traditional NSAIDs (3,10–12). Swan et al. (11) found a significant decrease in GFR in elderly persons receiving a low salt diet. It has been suggested that renal COX-2 expression is enhanced by low salt intake, and that it assists in the regulation of vascular tone and salt and volume homeostasis, mimicking a situation that more closely approximates the expected findings in patients who have more severely contracted effective circulating volume, e.g., in patients with congestive heart failure, diuretic use, or poor oral intake (10,11). In the present study, creatinine clearance was significantly diminished by the COX-2 inhibitor during the first 2 h after administration. This transient decrease in renal function was not detected by serum Cystatin C. As Cystatin C was assumed to be a sensitive marker for glomerular function (21,22), the missing effect on serum Cystatin C levels is most likely because of its limited ability to detect brief alterations of GFR. Furthermore, the present results are in agreement with observations that the effects of COX inhibitors on GFR are often independent of their effects on urinary electrolyte excretion (23). Changes in urinary excretion of albumin and α1-microglobulin were small, and not clinically important, suggesting no relevant glomerular or tubular damage.

Thus, although no risk population could be identified in the present study, our results and the accumulated scientific data imply that patients with concomitant diseases may experience clinically relevant decreases in GFR, which might be further aggravated by acute changes of the actual or effective circulating volume. In our study population no significant change of CVP was observed.

In contrast, paracetamol is generally perceived as a safe drug for acute pain management, especially in patients with impaired kidney function (24). It is supposed to act mainly by inhibition of central COX, and is believed to have only a weak potential to inhibit peripheral PG synthesis when administered at adequate dosages. With respect to the metabolism of paracetamol, there is less evidence for an influence on renal function.

The results of the present study support findings and recommendations from earlier studies, in which paracetamol has been demonstrated to have no effect on GFR in normal subjects (25), and is recommended as a safe analgesic for subjects with renal dysfunction (24,26,27).

In the present study, pain intensity and opioid consumption were observed as secondary objectives, and the sample size was expected to be too small to detect significant differences in the analgesic efficacy of the drugs. Treatment with paracetamol tended to decrease opioid consumption, although this trend did not reach a statistically significant level. This contrasts to clinical trials in acute postoperative pain, in which IV formulations of NSAIDs or COX-2 inhibitors were found to be equivalent or superior to paracetamol (4,28–30).

An important factor contributing to the observed analgesic efficacy of paracetamol in this study might have been the placebo effect. There is evidence that placebos activate endogenous opioid systems, thus producing placebo analgesia (31,32). In the present study, paracetamol was administered at 6 h intervals, while parecoxib was administered at 12 h intervals, as recommended by the manufacturers. Thus, the superior analgesic efficacy of paracetamol in this study might have been on the basis of expectations of pain relief and classical conditioning mechanisms, suggesting that frequent IV administration of shorter-acting analgesics can lead to additional placebo analgesic effects when compared with infrequent IV administrations of longer-lasting analgesics.

In conclusion, glomerular and tubular functions were transiently affected in all patients after orthopedic surgery; however, the differences between the treatment groups were small and not clinically relevant. Further studies are warranted to determine adverse renal effects of longer-lasting therapy with these drugs, especially in patients with renal impairment or concomitant diseases. Furthermore, the results of the present study suggest that different levels of analgesia by IV paracetamol and parecoxib might be related to the magnitude of placebo analgesic effects.

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