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Controlled-Release Oxycodone Versus Naproxen at Home After Ambulatory Surgery: A Randomized Controlled Trial

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ABSTRACT

Background: Strong opioids in the home setting after ambulatory surgery have rarely been studied for fear of hazardous adverse effects such as respiratory depression.
Objectives: We compared the efficacy of paracetamol/controlled-release (CR) oxycodone and paracetamol/naproxen for treatment of acute postoperative pain at home after ambulatory surgery. Secondary outcomes were adverse effects of study medication, treatment satisfaction, and postoperative analgesic compliance.
Methods: Patients undergoing ambulatory knee arthroscopy or inguinal hernia repair surgery (n = 105) were randomized into 3 groups: Group1 paracetamol/naproxen (n = 35), Group 2 paracetamol/CR oxycodone for 24 hours (n = 35), and Group 3 paracetamol/CR oxycodone for 48 hours (n = 35). Pain intensity at movement and at rest using a visual analog scale as well as satisfaction with postoperative analgesia and side effects were recorded for up to 48 hours postoperatively. Compliance with study medication was also assessed.
Results: For pain at movement and at rest, no significant differences were found between the paracetamol/naproxen group and either the paracetamol/CR oxycodone for 24 hours group (β = 2.6 [4.9]; $P = 0.597$) or the paracetamol/CR oxycodone for 48 hours (β = −1.7 [5.1]; $P = 0.736$). No major adverse effects of study medication were registered and satisfaction with postoperative pain treatment was high in all groups. Compliance was comparable across the groups. Despite clear instructions, 8 patients with the lowest pain scores did not use any of the prescribed pain medication.
Conclusions: Paracetamol/CR oxycodone and paracetamol/naproxen are equally effective in treatment of acute postoperative pain at home after ambulatory surgery with comparable patient satisfaction level. We suggest paracetamol/CR oxycodone to be a valuable alternative for the current paracetamol/naproxen gold standard, particularly in patients with a contraindication for nonsteroidal anti-inflammatory drugs. ClinicalTrials.gov identifier: NCT02152592.

Introduction

Adequate postoperative pain management is an essential part of perioperative care because postoperative pain results in patient discomfort and may decrease patient satisfaction.[1] More important, insufficient postoperative pain therapy is associated with an increase in perioperative morbidity and mortality and is an important risk factor for the development of chronic postsurgical pain.[2–4] It is also a common cause of delayed discharge and unanticipated hospital admission in outpatients.[5–7] In particular, patients who undergo abdominal operations (including inguinal hernia repair surgery), orthopedic surgery (including knee arthroscopy), or breast surgery seem to be at the highest risk for developing severe pain after day surgery.[8]

In the ambulatory setting, a multimodal approach to pain control combining intraoperative opioids, paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), weak opioids, and local and

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regional anesthesia has been advocated.[9,10] Strong opioids are often administered in the inpatient and chronic pain setting. However, strong opioids in the home setting after ambulatory surgery have rarely been studied because of fear for hazardous adverse effects such as respiratory depression.[11]

Paracetamol in combination with naproxen, an NSAID with a favorable adverse-effect profile,[12] comprise the standard multimodal pain treatment model at Maastricht University Medical Center+ for patients at home after ambulatory surgery. Nevertheless, NSAIDs are not always sufficiently effective,[13] have numerous contraindications, and consequently are not suitable in up to 25% of all patients.[14] Postoperative analgesic habits in the inpatient setting and the World Health Organization analgesic ladder suggest that strong opioids are more effective than NSAIDs and might therefore be an alternative. Oxycodone is a strong opioid that was used for the first time in Germany in 1917[15] and may display significant affinity to both μ-opioid and κ-opioid receptors.[16] In contrast to morphine, oxycodone possesses high oral bioavailability with less interindividual variation. As a result, the plasma concentrations following oral administration of oxycodone are far more predictable than after morphine.[17] Other beneficial characteristics of oxycodone are related to the lower incidence of adverse effects,[18] a rapid onset of action[18,19] and an absence of a ceiling dose.[19] Compared with immediate-release oxycodone, controlled-release (CR) oxycodone has the advantage of maintaining a therapeutic concentration for a more prolonged period, which may avoid peak-and-trough plasma concentrations and thus provide sustained pain relief with fewer side effects such as nausea and vomiting.[20–22] The primary objective of our study was to assess and compare the efficacy of paracetamol/CR oxycodone for 1 or 2 days and our current pain protocol (ie, paracetamol/naproxen) in the treatment of acute postoperative pain at home after painful day-case surgery. We hypothesized that ambulatory patients postoperatively treated with paracetamol/CR oxycodone for 1 or 2 days would achieve better pain relief at movement compared to patients treated with paracetamol/naproxen. The second goal was to assess adverse effects of study medication, treatment satisfaction, and patients' analgesic adherence in the outpatient setting.

Materials and Methods

After obtaining approval from the Medical Ethics Committee of Maastricht University Medical Center+ and written informed consent, 105 patients scheduled for painful ambulatory surgery (ie, knee arthroscopy and unilateral open or laparoscopic inguinal hernia repair) were enrolled in an open randomized controlled trial (RCT) at our preassessment clinic. This trial was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human beings.

Eligible patients were aged 18 to 70 years and had American Society of Anesthesiologists (ASA) physical status I or II. Exclusion criteria were cognitive impairment, preoperative pharmacologic pain treatment, allergy to or a contraindication for taking the study medication (eg, paracetamol, oxycodone, naproxen, or another NSAID), porphyria, pregnancy, lactation, history of severe renal, hepatic, pulmonary, or cardiac failure, current symptoms or history of gastrointestinal bleeding, ileus, chronic obstipation, history of substance abuse, or use of medication with a suppressive effect on the central nervous system. Dropout criteria were surgical complications leading to either resurgery or unanticipated hospital admission. Patients were enrolled by a study nurse, consecutively included, and randomized using a computer-generated list. Three study groups were included, of which the first group served as control group and the second and third as intervention groups: Group 1 paracetamol/naproxen (PCM/NAPR), where patients were assigned to postoperative analgesia using naproxen 500 mg orally BID for 48 hours postoperatively (n = 35); Group 2 paracetamol/CR oxycodone for 24 hours (PCM/Oxy24h), where patients received CR oxycodone 10 mg orally BID for 24 hours (n = 35); and Group 3 paracetamol/CR oxycodone for 48 hours (PCM/Oxy48h), where patients were postoperatively treated with CR oxycodone 10 mg orally BID for 48 hours (n=35). All patients also received paracetamol 1000 mg 4 times a day for 48 hours postoperatively and were ordered to take their analgesics according to a fixed-dose schedule to prevent rather than to cure pain. To obtain approval from our Medical Ethics Committee, naproxen as rescue medication was obligatory for patients in Groups 2 and 3. Because of organizational difficulties, this RCT could not be made double-blind. Upon hospital admission, patients received a pain diary, a stamped addressed envelope, and instructions for use. Patients were asked to provide a detailed medical history and demographic information, including age, sex, body mass index, ASA classification, and history of postoperative nausea and vomiting (PONV). Furthermore, baseline preoperative pain measurement using a numeric rating scale (0–100) was assessed verbally. Thirty minutes before surgery, premedication with oral paracetamol 1000 mg was given to all patients. Type and duration of surgery and anesthesia were registered. Appropriate type of anesthesia and antiemetic therapy was chosen by the attending anesthesiologist. Postoperative pain at movement and at rest was measured by a visual analog scale (VAS) (0–100). PONV, pruritus, urine retention, pyrosis, cardiorespiratory complaints, abdominal complaints, and bleeding were assessed in the postanesthetic care unit (PACU) and in the surgical holding area before discharge. Acute postoperative pain (VAS $\geq$40) in the PACU was treated with subsequent bolus injections of piritramide 0.1 mg/kg intravenously until pain relief was satisfactory. Before hospital discharge, patients received the study medication and instructions for use.

Recovery after discharge was assessed using a diary for up to 48 hours after surgery. Three times a day, patients rated pain at movement and at rest (using a 0–100 VAS), fatigue, PONV, pruritus, micturition problems, pyrosis, constipation, and abdominal complaints. Overall satisfaction with postoperative analgesia was assessed (0 = not satisfied at all and 10 = very satisfied), and patients were also asked whether they had contacted a general practitioner or hospital postoperatively. Furthermore, compliance with prescribed analgesia was assessed 3 times a day by checking whether patients used the study medication as prescribed and the use of other pain medication. Analgesic compliance was subdivided in 3 categories: always = full compliance, sometimes = partial compliance, and never = no compliance.

Statistical analysis

The statistical power analysis was based on a calculation using an SD of 22 for the postoperative VAS scores. To detect a difference of 15 with a power of 0.80 and $\alpha = 0.05$, 35 patients in each group were required. Baseline data and secondary outcomes were analyzed using the Student *t* test for parametric data, the Mann-Whitney *U* test for nonparametric pain scores, and the χ^2 test for categorical data. Missing baseline values (ASA and preoperative pain) were imputed. Multivariate analysis of the primary outcome, VAS scores of postoperative pain at movement and rest, was performed using a random intercept model with autoregressive covariance structure. For multivariate analysis the following covariables were assessed: baseline pain (numeric rating scale), age, sex, body mass index, ASA classification, type of surgery, duration of surgery, type of anesthesia, and pain (VAS) at PACU, holding, and

day of surgery 20 hours. Differences between the PCM/NAPR group versus the PCM/Oxy24h group and the PCM/Oxy48h group as a function of time were assessed with the PCM/Oxy24h treatment and PCM/Oxy48h treatment, and time fixed effects. Regression coefficients (β) and SD are presented and reflect the change in pain for each unit of change in the predictor. The data were analyzed according to the intention to treat principle. All analyses were performed using the Statistical Package for the Social Sciences (version 18, IBM-SPSS Inc, Armonk, New York). A P value < 0.05 was considered statistically significant.

Results

A flow chart of patient selection and drop out is presented in Figure 1. Four patients were hospitalized, but not as a result of surgical complications. Patients included underwent surgery between October 2007 and March 2009. Fifty-nine patients received spinal anesthesia with either hyperbaric bupivacine 0.5% (10–15 mg) or plain lidocaine 2% (60–80 mg). In 3 cases, spinal anesthesia was converted to general anesthesia. Forty-six patients received general anesthesia. Anesthesia was generally induced with propofol (1.5–2 mg/kg IV) and sufentanil (0.1–0.3 μg/kg). After a laryngeal mask airway was inserted, anesthesia was maintained with sevoflurane. Wound infiltration with local anesthesia was performed in 15 patients (Table I). Postoperatively, 10 patients who underwent general anesthesia received piritramide (Table I). With regard to baseline and surgery characteristics, there were no statistically significant differences between the PCM/NAPR group and the 2 PCM/Oxy groups (Table I).

For pain at movement, no significant difference was found between the PCM/NAPR group and either the PCM/Oxy24h group (β = 2.6 [4.9]; P = 0.598) or the PCM/Oxy48h group (β = −1.7 [5.1]; P = 0.737) (Figure 2). Time course (with decrease in pain over time [hours]) (β = −0.4 [0.03]; $P < 0.001$) and acute postoperative pain (VAS ≥40) directly measured at the PACU was a significant risk factor (β = 0.3 [0.09]; P = 0.004) for pain at movement. In addition, there was an increased risk for pain at movement in patients who underwent inguinal hernia repair compared with arthroscopy (β = 9.2 [4.9]; P = 0.064). For pain at rest, no significant difference between the study groups and control group was found. Besides a significant decrease in pain

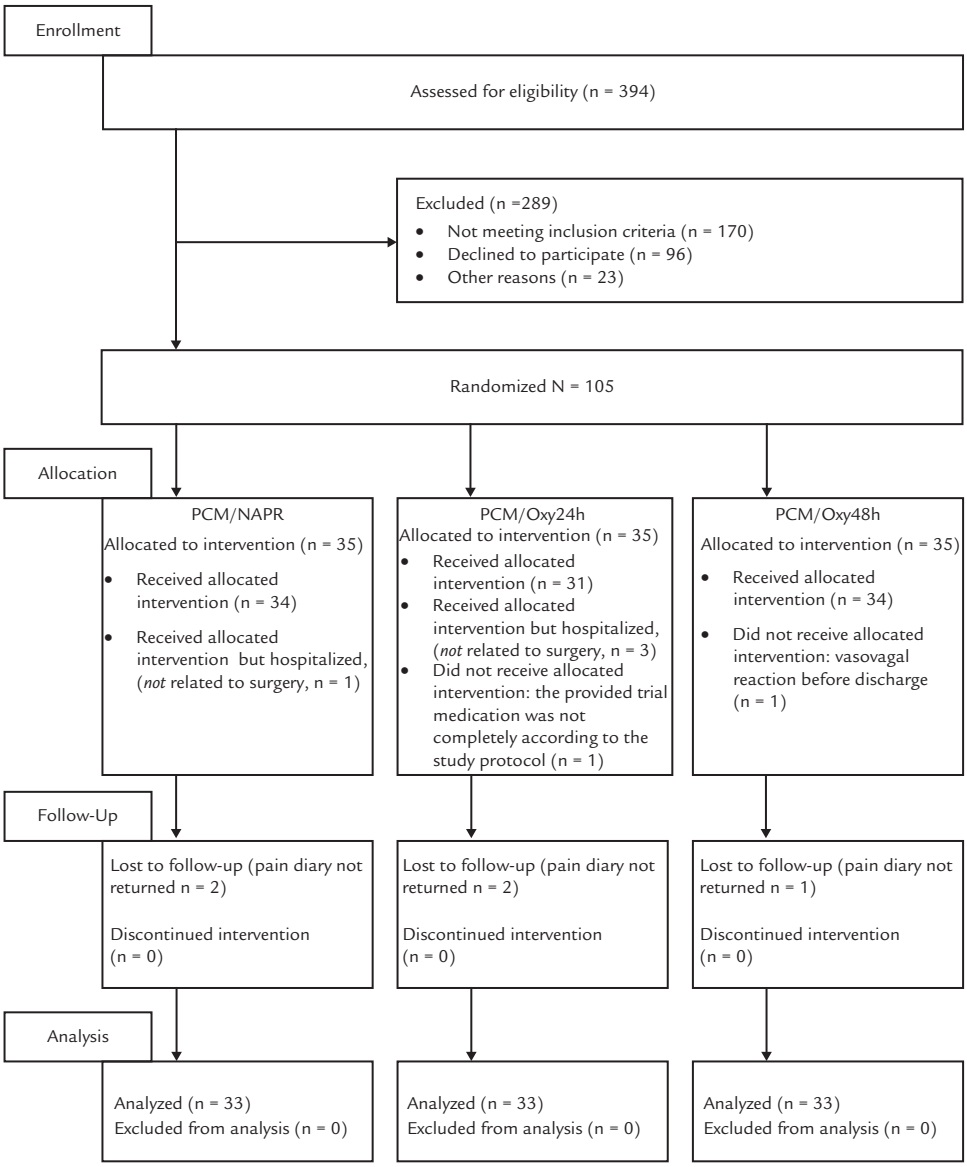

Figure 1. Study flow chart. Analysis according to intention-to-treat principle. PCM/NAPR = paracetamol/naproxen; PCM/Oxy24h = paracetamol/oxycodone for 24 hours; PCM/Oxy48h = paracetamol/oxycodone for 48 hours.

Table I
Baseline and perioperative characteristics.*

Characteristic	PCM/NAPR (n = 35)	PCM/Oxy24h (n = 35)	PCM/Oxy48 (n = 35)
Age, y	45.4 (14.2)	45.1 (14.2)	48.5 (10.2)
Sex male/female	24/11	26/9	27/8
Body mass index	25.6 (3.3)	25.7 (3.8)	26.0 (3.0)
American Society of Anesthesiologists classification I/II	29/6	24/11	26/9
Pain baseline†	3.6 (0–22.8)	3.0 (0–13.2)	5.0 (0–30.0)
Surgery			
Laparoscopic inguinal hernia repair	6	6	5
Open inguinal hernia repair	2	2	3
Arthroscopy‡	27	27	27
Duration of surgery, min	46 (14)	50 (21)	47 (17)
Anesthesia			
General/ + local	11/+ 5	17/+ 1	8/+ 4
Spinal/ + local	16/+ 1	15/+ 2	20/+ 2
Conversion spinal to general	2	0	1
Piritramide postoperative			
PACU IV	5	7	2
PACU IM	0	0	2
PACU IV + IM	0	1	0
Holding IM	0	2	0

IM = intramuscular; IV = intravenous; PACU = postanesthetic care unit.
* Values are presented as number, mean (SD), or median (interquartile range).
† Based on numerical rating scale of 0 to 100.
‡ Anterior cruciate ligament reconstruction surgery was not included.

over time, the assessment of covariables revealed an increased body mass index as a significant risk factor for pain at rest. None of the other covariables, including type of anesthesia (general vs spinal), had a significant effect on either pain at movement or pain at rest.

Numbers of self-reported complications were comparable for all groups, except for constipation that was reported to a significantly less degree in the PCM/Oxy24h group compared with the PCM/NAPR group (**Table II**). No life-threatening respiratory depressions or other major adverse effects of study medication were reported. Satisfaction with postoperative pain treatment was high: mean (SD [range]) 8.3 (1.7 [4–10]), 8.1 (1.5 [4–10]), and 8.6 (1.1 [6–10]) for the PCM/NAPR, PCM/Oxy24h, and PCM/Oxy48h group, respectively. Use of rescue medication was reported by only 3 patients, all of whom were in the PCM/Oxy24h group. Three patients in the PCM/NAPR group used unprescribed extra pain medication.

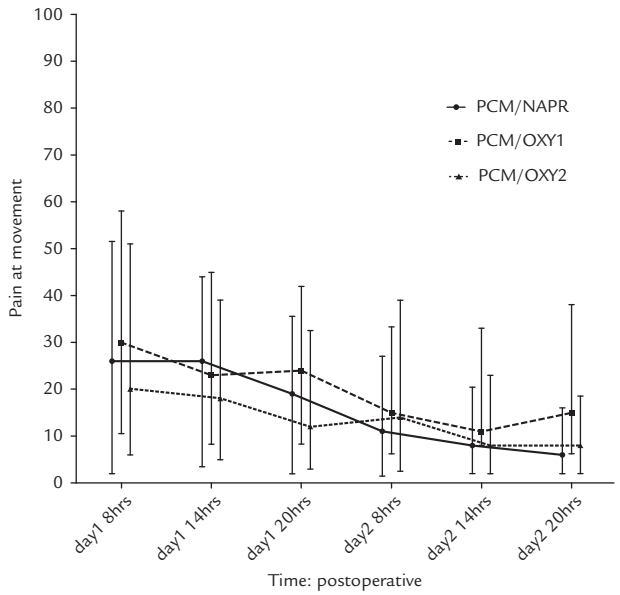

Figure 2. Pain at movement on Postoperative Days 1 and 2. Median (interquartile range), based on visual analog scale rating (0–100). PCM/NAPR = paracetamol/naproxen; PCM/OXY1 = paracetamol/oxycodone for 24 hours; PCM/OXY2 = paracetamol/oxycodone for 48 hours.

Table II
Complications on Postoperative Days 1 and 2.*

Complication	PCM/ NAPR	PCM/ Oxy24h	PCM/ Oxy48h
Fatigue	23 (66)	19 (54)	25 (71)
Nausea	5 (14)	7 (20)	8 (23)
Vomit	0 (0)	0 (0)	1 (3)
Micturition problems	0 (0)	0 (0)	1 (3)
Constipation	12 (34)	4 (11)†	11 (31)
Pyrosis	3 (9)	3 (9)	1 (3)
Abdominal complaints	5 (14)	7 (20)	4 (11)
Pruritus	7 (20)	3 (9)	8 (23)
Contact general practitioner or hospital	3 (9)	0 (0)	0 (0)

PCM/NAPR = paracetamol/naproxen; PCM/Oxy24h = paracetamol/oxycodone for 24 hours; PCM/Oxy48h = paracetamol/oxycodone for 48 hours.
* Number (%) of patients reporting complications.
† $P = 0.041$ compared with PCM/NAPR group.

Compliance was similar across groups. Despite clear instructions during the informed consent procedure and before discharge, 8 patients did not use any of the prescribed pain medication. When associated with their postoperative pain scores, it appeared that these 8 patients did not experience postoperative pain (**Table III**).

Discussion

A multimodal analgesic regimen consisting of paracetamol/CR oxycodone for either 24 or 48 hours immediately after surgery was found to be equally effective in reducing postoperative pain compared with paracetamol/naproxen in an adult population undergoing ambulatory knee arthroscopy or inguinal hernia repair surgery. No respiratory depressions or other major adverse effects of study medication were reported, and the incidence of opioid-related adverse effects like PONV was comparable in the 3 groups. Overall satisfaction with postoperative analgesia was high across all 3 groups. Although the analgesic efficacy and safety of oral oxycodone at home after surgery has already been confirmed in 1 study,[23] ours is the first RCT to demonstrate equipotent analgesic efficacy of a combination of paracetamol and CR oxycodone with our standard multimodal pain management at home after day surgery; that is, paracetamol with a NSAID. Paracetamol/CR oxycodone seems to be a valuable alternative to paracetamol/naproxen, in particular for those patients with a contraindication for NSAIDs, which occurs in up to 25% of all patients.[14]

Table III
Compliance and maximum pain scores on Postoperative Days 1 and 2 in relation to compliance.*

Compliance	PCM/NAPR	PCM/Oxy24h	PCM/Oxy48h
Full compliance N/max VAS*†	17/96	19/81	22/76
Partial compliance N/max VAS	13/77	11/93	8/79
No compliance N/max VAS	3/2	2/20	3/7
Missing N	2	3	2

N = number; VAS = visual analog scale.
* Medication use as prescribed: always = full compliance, sometimes = partial compliance, never = no compliance.
† Pain at movement, maximum score per group (VAS of 0–100).

The potency of oxycodone to reduce postoperative pain is well known.[24] In particular, CR oxycodone seems to possess an excellent profile for postoperative pain relief characterized by producing a relatively constant serum opioid level with sustained pain relief and fewer side effects.[20,22] Two studies have compared intravenous patient-controlled analgesia with an opioid, a gold standard for the management of pain after major surgery, with oral CR oxycodone after major surgery in an inpatient setting.[21,22] Both studies demonstrated a similar level of pain relief in the 2 study groups with a lower incidence of PONV in the CR oxycodone group and without occurrence of any serious adverse event. They concluded that oral CR oxycodone is a less expensive, more convenient, and safe analgesic alternative compared with intravenous patient-controlled analgesia with an opioid. In 3 other studies, oral CR oxycodone was compared with epidural analgesia to reduce postoperative pain.[25–27] These studies also found pain relief to be satisfactory in both study groups, with a similar incidence of PONV and without occurrence of serious adverse effects. High patient satisfaction with oral CR oxycodone after laparoscopic hysterectomy is also confirmed.[28]

Although one could presume a higher incidence of opioid-related adverse effects in the 2 CR oxycodone groups, no differences in adverse effects between the 3 study groups were found. However, our study was not powered a priori to detect significant differences in the incidence of adverse effects. Nonetheless, our data are consistent with previous studies. In an RCT comparing the effect of oral ibuprofen and celecoxib in preventing pain after ambulatory surgery with placebo, White et al[29] could not detect any difference in incidence of PONV despite the use of 2 times more rescue opioid analgesic medication in the placebo group. Another study also failed to detect significant differences in postoperative side effects between ibuprofen and paracetamol plus codeine, except for significantly more constipation in the second group.[30] Furthermore, several investigators have demonstrated a reduced incidence of side effects of CR oxycodone compared with other opioids.[20–22] Finally, pain itself has been associated with nausea and other opioid-related adverse effects, and effective treatment of pain can diminish nausea.[31]

One of our secondary outcomes was compliance with postoperative pain medication. The literature reports that noncompliance by chronic pain patients using analgesia is a frequent and well-known problem.[32,33] However, to our knowledge, this is the first study to investigate compliance of patients to acute postoperative pain medication. Our study shows that analgesic adherence is related to postoperative pain after ambulatory surgery, independent of the type of pain medication (ie, NSAIDs or opioids). Although we cannot prove a causal relation, patients with little or no pain are obviously not triggered by a pain stimulus to take their pain medication. Our observations are supported by findings from studies on patients with chronic pain. Two large studies demonstrated that higher levels of pain correspond to more regular analgesic use.[34,35] In contrast, a cross-sectional clinical survey in 1407 patients with chronic noncancer pain pointed out that there is a small but significant inverse relationship between analgesic adherence and pain intensity.[36] Future studies are needed to clear up this inconsistency.

There are several limitations to our study. First, because of organizational difficulties, this RCT was not double-blind. Therefore, there is potential risk for information bias. Second, secondary end points (ie, adverse effects of pain medication, patient satisfaction, and compliance) did not reach statistical significance, except for constipation. However, it should be emphasized that our study was not powered for secondary outcomes. Third, prescription of rescue medication was only provided in the 2 CR oxycodone groups. Moreover, rescue medication consisted of naproxen. Evidently, this anomaly carries great risk for overestimation of the efficacy of pain relief in the 2 CR oxycodone groups. Nevertheless use of rescue medication was reported by only 3 patients, all of them in the PCM/Oxy24h group. Also 3 patients in the PCM/NAPR group used extra pain medication. Fourth, anesthesia during surgery was not standardized. Obviously, there is a potential hazard for treatment bias due to possible differences in amounts of analgesic and antiemetic drugs used intraoperatively. Nevertheless, distribution of spinal versus general anesthesia over the 3 study groups was identical. Furthermore, all patients received additional intravenous piritramide in the PACU until satisfactory pain relief was reached.

Conclusions

Paracetamol and CR oxycodone for 24 or 48 hours were both clinically equivalent to the current paracetamol/naproxen gold standard in multimodal pain treatment for patients at home after ambulatory surgery (ie, paracetamol and naproxen). Therefore, treatment with paracetamol and CR oxycodone is a valuable alternative to paracetamol and naproxen, particularly in patients with a contraindication for NSAIDs.

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B. Stessel was responsible for the literature search, statistical analyses, data interpretation and writing of the paper. M. Theunissen was responsible for the data collection, statistical analyses, figure creation and writing of the paper. A.A. Fiddelers was responsible for the writing of the paper. E.A. Joosten was responsible for the writing of the paper. A.G. Kessels was responsible for the statistical analyses. H.-F. Gramke was responsible for the study design. M.A.E. Marcus was responsible for the study design.

Conflict of interest statement

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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