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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