Intravenous oxycodone compared to morphine for post-operative opioid-related adverse events in opioid naïve patients: a prospective randomized controlled trial

philippe cuvillon (✉ philippe.cuvillon@chu-nimes.fr)

Hopital Universitaire Caremeau <https://orcid.org/0000-0002-4424-4280>

Sandrine Alonso

Hopital Universitaire Caremeau

Joel Lhermite

Hopital Universitaire Caremeau

Vanessa Reubrecht

Assistance Publique - Hopitaux de Paris

Lana Zoric

Hopital Universitaire Caremeau

Nathalie Valees

Hopital Universitaire Caremeau

jean-luc. faillie

Centre Hospitalier Regional Universitaire de Montpellier

Pascal Kouyoumdjian

Hopital Universitaire Caremeau

Christophe Boisson

Hopital Universitaire Caremeau

mathieu raux

Assistance Publique - Hopitaux de Paris

olivier langeron

Assistance Publique - Hopitaux de Paris

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Abstract

Background: Intravenous oxycodone compared to morphine for postoperative pain relief is controversial. The purpose of this study was to assess opioid-related adverse events of oxycodone versus morphine in opioid-naïve patients after orthopaedic surgery.

Methods: Patients scheduled for total hip arthroplasty under general anesthesia combined with a multimodal analgesia (acetaminophen, nonsteroidal anti-inflammatory) were randomized in a triple-blinded trial to postoperative pain treatment with either intravenous oxycodone or morphine (potency ratio 1:1). After surgery, patients received similar drug regimen for titration in the postoperative care unit (bolus 2-3 mg, 5 min period, when pain score was $>3/10$) followed by an intravenous patient controlled analgesia (bolus 1 mg, lockout time 7 min) postoperatively. The primary outcome was number of patients with ≥ 1 opioid-related adverse events within the first 24 hours (at least one of the following complications: nausea, vomiting, respiratory depression, pruritus, urinary retention requiring evacuation, allergy, hallucination). Secondary outcomes included pain scores, opioid consumption. Patients were followed up to 4 months.

Results: The intention-to-treat analysis included 241 patients with similar characteristics. There were 55 patients with at least one opioid-related adverse events in oxycodone group versus 46 in morphine group (48% vs 40%, $p=0.19$; relative risk= 1.22 [0.91; 1.63]). Oxycodone versus morphine requirements were respectively: 6 [0-11] versus 8 [0-12] mg ($p=0.06$) for titration, 15 [8-26] versus 8 [5-16] mg ($p=0.001$) for PCA dose, and 22 [12-37] mg versus 19 [11-28] mg for the titration and PCA accumulated consumption ($p=0.048$). During the first 24 hours, there were no other differences in secondary outcomes between both drugs for (respectively oxycodone versus morphine in %): nausea (15 versus 13), vomiting (5 versus 5), urinary retention (20 versus 12) and pain scores.

Conclusion: This study demonstrated that oxycodone required lower doses for titration in postoperative care unit, but did not significantly reduce opioid-related adverse events within the first 24 hours compared to morphine.

Background

Multimodal analgesic approach (including anti-inflammatory drugs, regional analgesia and local infiltration) have been recently developed to enhance post-operative rehabilitation and pain relief. This approach may lead to decreased narcotic consumption [1–4]. Despite the increase in clinical research on non-opioid analgesics, many patients still complain of severe postoperative pain and require opioid initiation (intravenous or oral) in the postoperative care unit (PACU) or in the first few days postoperatively [5–7]. In these situations of severe postoperative pain, the use of intravenous morphine for titration in PACU followed by an i.v. Patient-Controlled Analgesia (PCA) remains the gold standard as it provides rapid and effective pain relief [5–7].

Since the 1990s, oxycodone has been proposed as an alternative to morphine, because by acting on the μ 1-receptors and on the κ -2-opioid agonist, it leads to a better anti nociceptive effect for post-operative pain relief or cancer-related pain [8–14].

Several studies have shown that per os oxycodone was associated with better pain control, less serious opioid-related adverse events (ORAEs) and a faster onset of action due to a better pharmacokinetic profile: higher oral bioavailability and lower plasma variability [15–19]. However, controversies have arisen as a result of recent clinical studies and meta-analysis that have shown that per os oxycodone did not reduce adverse events and pain relief. Not to mention that appetite for oxycodone itself is decreasing, due to concerns about addiction and the bad reputation that this drug has acquired in opiate-related crises [11, 13, 14, 19–23].

As with the oral route, the intravenous use of oxycodone remains debated because the number of studies on the subject is limited and the potency ratio of oxycodone to morphine (1:1 or 1:2) unresolved [16, 24]. Moreover, no large clinical studies have clearly demonstrated the benefit/risk (ORAEs) of i.v. oxycodone versus morphine. The hypothesis of this study was that i.v. oxycodone (versus i.v. morphine) would reduce ORAEs, assessed 24 hours post-operatively. At the same time, pain levels were as well evaluated (secondary outcome).

Methods

Institutional Human Committee, consent and setting

In accordance with the French legislation, the present study was approved by the institutional human investigation committee (Comité de Protection des Personnes, CPP, Nîmes, France, EudraCT: 2011-004140-22, Chairperson Prof T. Lavabre-Bertrand) on 7 January 2012 and was registered prior to enrolment on ClinicalTrials.gov (NCT 01536301) [25]. Study was conducted in two French University centres (APHP, La Pitié-Salpêtrière Paris, France; Hôpital Carémieu, Nîmes, France). The CONSORT (Consolidated Standards of Reporting Trials) recommendations for reporting randomized trial were followed. The analysis occurred after patient enrolment was completed.

Written informed consent was obtained from all participants before inclusion.

Study design and Patients

This was a prospective, randomized, triple blinded (Participant, Investigator, Outcomes Assessor), 1:1 ratio, double center control trial. Patients > 18 yrs scheduled for unilateral elective total hip arthroplasty (posterolateral surgical approach) under general anesthesia and opioid naïve were eligible and approached by the surgeon or the investigators. Exclusion criteria were: refusal to participate, age > 80 yrs, weight < 50 or > 100 kg, emergency or bilateral surgery including hip fracture, any regional anesthesia or analgesia (including: wound infiltration, peripheral nerve block, epidural or spinal injection), cognitive disorders (delirium, dementia...), pregnancy, patients with alcohol or drugs abuse, uncontrolled epilepsy,

patients unlikely to be fully cooperative during the study, participation in another study within the previous 30 days. Patients with chronic pain and/or reporting any allergy or contraindication to study drug (creatinine clearance $< 50 \text{ mL min}^{-1}$, Cockcroft formula), hepatic insufficiency (transaminases and/or alkaline phosphatases > 3 times of upper normal value, and/or prothrombin time $< 70\%$ of control), acute or chronic respiratory insufficiency ($\text{Spo}_2 < 94\%$ in ambient air), porphyria, intracranial hypertension, or ileus were not included. Finally, patient already taking narcotics or opioid, opiate agonist (codeine, dextromoramide, dihydrocodeine, oxycodone per os, tramadol, morphine-like antitussive...) or agonist-antagonists (buprenorphine, nalbuphine, pentazocine) were not included.

Study Drug, randomization and blinding

Patients were randomly assigned to the oxycodone group or morphine group using computer-generated random numbers created by the study statistician using a 1:1 randomization ratio. Group allocations were concealed in sequentially numbered opaque envelopes, which were opened by the research nurse just after the start of surgery. Randomization for the two centers were performed using blocks of randomization (8 patients per block). Pharmacy personnel not involved in clinical care of the patient prepared drug solutions. The morphine and oxycodone vials were similar, allowing a double-blinded design. In the case of a serious adverse event, the double-blind could be removed. Patients, surgeons, attending anesthetists, nurses and investigators were blinded to group assignment until data analysis.

Drug solutions were prepared using:

- 95 mL of saline solution
- 5 mL solution of study drug (20 mg mL^{-1}): 100 mg of oxycodone or morphine

From the 100 mL drug solutions ($1 \text{ mg: } 1 \text{ mL}$), 20 mL of the solution were transferred in 20 mL syringe and used for titration in PACU. The remaining 80 mL were used for the patient-controlled analgesia (Gemstar, Abbott Laboratories, Abbott Park, IL, USA) for a 48-h period. The settings for PCA were boluses of 1 mL with a lockout interval of 7 min without infusion limit. No basal infusion was used.

Study drug administration and background analgesic protocol

Thirty minutes before the end of the surgery, all patients received i.v. 1 g paracetamol over 15 minutes, 100 mg ketoprofene and 20 mg nefopam. First two were continued for 48 hours (at 6-h intervals for paracetamol and 12-h for ketoprofene).

In the PACU, patients experiencing pain with a numeric pain rating scale (NRS, 0–10) > 3 were given an i.v. manual titration of 3 mL of study drug (2 mL when body weight $< 60 \text{ kg}$) at 5-min intervals until a NRS score ≤ 3 was obtained according to a protocol already used routinely in our PACU. All nurses in the PACU had been trained to assess pain using unidimensional scales and to perform opioid titration. At this time, the i.v. PCA with study drug (80 mL) was connected to the patient for 48 h.

Drug titration was stopped if the patient had a respiratory rate lower than 12 breaths min^{-1} and/or an SpO_2 lower than 94% and/or experienced a serious adverse event related to opioid administration (allergy with cutaneous rash, vomiting, severe pruritus) and also if the patient was asleep. In case of severe ventilatory depression (respiratory rate, $\text{RR} < 10$ breaths min^{-1}) an intravenous bolus of 0.04 mg naloxone was administered until RR was greater than 12 breaths min^{-1} , and this was defined as a severe ORAEs.

General anesthesia and perioperative management

In both groups, oral premedication was given 1 h before surgery (hydroxyzine 1 mg kg^{-1}). General anesthesia was induced with propofol (2–3 mg kg^{-1}), sufentanil (0.3 $\mu\text{g kg}^{-1}$), and cisatracurium (0.3–0.5 mg kg^{-1}). Airway was maintained with tracheal tube and the lungs were ventilated with a mix of oxygen–air (50/50). Tidal volume and respiratory rate were set to maintain end tidal volume CO_2 between 35 and 40 mmHg. A 5-cm H_2O positive end expiratory pressure was set. Anesthesia was maintained with sevoflurane 1–2% and additional intravenous sufentanil (5–10 μg) upon request i.v. fluid administration was ringer lactate $< 10 \text{ mL kg}^{-1} \text{ h}^{-1}$. Urinary intra-operative catheter was not placed.

At the end of surgery, patients were extubated and transferred to the PACU. Prevention of nausea or vomiting was based on Apfel score (female sex, non smoker, history of motion sickness or postoperative nausea and vomiting, postoperative opioid treatment: 0 to 4 points). For patients with score 1 or 2, i.v. dexamethasone 0.1 mg. kg^{-1} was injected after the induction of anesthesia, followed with i.v. 4–8 mg ondansetron for score > 2 . The Aldrete's scoring system was used for determining when the patient can be discharged (score: 0–10: a score ≥ 9 was required for discharge).

Over the first 48 hours post-operative period, patients in both groups were managed similarly and standardized: early oral intake and post-operative rehabilitation, i.v. ondansetron (4 mg) was injected in case of nausea or vomiting. At the end of the PCA perfusion (48 h), oral acetaminophen, ketoprofen and tramadol (as rescue medication) were given to the patient for pain relief. Patients were discharged from the surgical ward at the discretion of the surgeon.

Clinical assessment

Preoperative evaluation was performed the day before surgery, including: NRS pain score at rest and at on movement (0–10), DN4 score (0–10), walking ability (m), medical diseases, physiological parameters (blood pressure, heart and respiratory rate, pulse oxymetry), biological variables (Hemoglobin, creatinine clearance). Pain intensity and adverse events were assessed in PACU and every 6 h over the study period (48 h). The nurse staff evaluated patient pain intensity using a NRS at rest and on movement (hip mobilization). When the patient was asleep, no attempt was made to wake him up, and the patient was considered as having analgesia and a score of 0 mm was assigned to the patient. Total drug administration in PACU and over the 24 hours were recorded.

ORAEs. arising from the analgesic protocol were systematically assessed in PACU and surgical ward by nurses in charge of the patient (blinded to group assignment): nausea, vomiting, drowsiness, dizziness, headache, sweating, itching, confusion/hallucination, pruritus, sedation, arterial hypotension (mean arterial pressure < 80 mmHg), respiratory depression. These outcomes were viewed as binary (Yes/No), every 6 h after PACU. Arterial oxygen saturation (pulse oximetry), heart and respiratory rates and blood pressure was recorded every 6 h. Desaturation was considered pulse oxygen saturation < 94%. A respiratory rate < 10 breaths/min was considered as respiratory depression. Heart rate > 120 bpm and < 50 bpm defined tachycardia and bradycardia, respectively. Sedation was defined by a Ramsay scale > 2.

After 4 months, all patients were called and questioned for pain, DN4 score (0–10 points), satisfaction about pain after surgery (using a NRS: 0–100) and other adverse events medical or surgical complications [26].

Endpoints

The primary endpoint was the rate of opioid-related adverse effects from start of titration to 24 h. As previously described, the following ORAEs were the presence/absence of at least one of the following complications: nausea, vomiting, respiratory depression, pruritus (itch), urinary retention requiring evacuation (spontaneous voiding impossible despite bladder volume > 400 ml measured by ultrasound), allergy (skin reaction), hallucination (perception without object). Ventilator depression was defined as RR below 10 min⁻¹ or need for naloxone administration. Sedation was defined as a Ramsay score above 2 but was not considered as an ORAEs

The secondary end-points were: the time to achieve pain relief in the PACU, the number of patients with post-operative severe pain, the number of patients who required titration, the duration of stay in the PACU period, the consumption of opioid during the PACU and PCA periods, the number of demands for opioid and the number of boluses received during the PCA period, the total dose administered over 24 h, pain scores during the PACU and the PCA periods, and the patient satisfaction assessment.

Sample Size Calculation

The sample size was calculated based on the ability to detect a significant difference in adverse events between oxycodone versus morphine groups with a difference in the ORAEs occurrence of 50% (32% vs 16%) with 80% power, based on previous study with morphine.¹⁻¹⁰ The level of significance was set at two-sided $\alpha = 0.05$ to support the hypothesis that ORAEs oxycodone group were different than that in the morphine group. Using these assumptions, we calculated a sample size of 222 patients (111 patients per group). We increased the number to 246 patients (123 per group) to account for 10% loss to follow-up.

Statistical analysis

Statistical analysis was conducted using SAS (9.4; SAS Inc., Cary NC). An intention-to-treat analysis was performed without any interim analysis. Statistical results were expressed with mean (SD) or median [25–75 IQ] according to the distribution. The numbers and associated percentages were given for categorical variables. Comparisons of continuous variables between the groups were performed using a

student's t test or Wilcoxon-Mann-Whitney test according to the distribution. Categorical variables were compared between groups by χ^2 or Fisher's exact test.

All statistical tests were conducted as 0.05 two-sided tests.

Results

Population of the study

From June 2012 to July 2016, 623 patients scheduled for primary unilateral total hip arthroplasty were screened and 246 patients were randomized (Fig. 1). After randomization, 5 patients withdrew from the study: 4 for protocol violation, one for a cancelled surgery. These patients were not included in the final analysis ($n = 241$). Three patients discontinued the treatment. At 4 months, 102 and 106 patients in oxycodone and morphine group completed their end-of-study visit, respectively.

Baseline characteristics, preoperative pain, physiological and biological parameters, type of surgery and anesthesia were similar in both groups (Table 1). Premedication (64 versus 70 patients), intra operative sufentanil administration (40 [30–45] versus 35 [30–45] μg), median perioperative i.v. fluid (1225 vs 1000 mL) and number of patients requiring red blood transfusion (1 vs 2) were well balanced between groups. Moreover, the number of patients receiving iv ondansetron (6 vs 3) or i.v. dexamethasone (72 vs 65) during general anesthesia was similar.

Primary outcome (Table 2)

The number of patients with at least one ORAEs was similar in both group: 55 (48%) in oxycodone group versus 46 (40%) in morphine group ($p = 0.19$) with a relative risk = 1.22 [0.91; 1.63]. Nausea and vomiting were the main ORAEs in 23% patients in both groups in PACU (Table 2). Respiratory depression was the first ORAEs in PACU (all patients: 21%), without any respiratory complication after PACU. Urinary retention was the first ORAEs in both groups after PACU discharge within the first 24 hours (all patients: 15%) (Table 2).

Secondary outcomes

The initial NRS pain at rest in PACU was similar in both groups: 4 [0–6] for oxycodone group vs 4 [0–7] for morphine group ($p = 0.7$). The number of patients requiring titration (NRS pain $> 3/10$) was comparable for both groups. For these patients, the number of boluses to obtain a NRS pain $< 3/10$ was reduced in oxycodone group as compared with morphine group ($p = 0.03$), but no difference was observed for the time of titration and the PACU time discharge (Table 3). Time < 45 min to get a NRS pain $< 3/10$ was recorded for 76 (95%) patients in oxycodone group versus 75 (85%) in morphine group ($p = 0.036$) with a relative risk oxycodone versus morphine = 0.34 [0.12; 0.99].

The number of ORAEs (Table 2), the number of sedated patients (1 versus 1), and the number of patients requiring termination of morphine titration (2 versus 3) were similar between groups. Morphine or

oxycodone requirements during the PCA period were less in morphine group, but the total dose of both drugs administered within the first 24 h were significantly different between groups (Table 3). Over the study period, similar NRS pain at rest or movement were recorded for both groups, with a median score < 3/10 at each time (H6, 12, 18, 24, 30, 36, 42, 48) (Fig. 2A and 2B). Patient satisfaction at the end of PCA period was not different in both groups (77 ± 26 in morphine group versus 73 ± 27 in oxycodone group, $p = 0.42$).

At the end of the follow up period (4 month), the number of patients included in this analysis was 51 in oxycodone group and 53 in morphine group. No difference was observed regarding DN4 scores ($p = 0.78$), median NRS pain score at movement ($p = 0.67$) and satisfaction ($p = 0.47$) (Table 3).

Discussion

This prospective triple blinded study demonstrated that intravenous oxycodone did not lead to less opioid-related ORAEs within the first 24 hours after major orthopedic surgery as compared with morphine. Post-operative pain relief and patient satisfaction were similar between the two drugs.

In this prospective, randomized, large-scale study of patients, we hypothesized that oxycodone would reduce opioid-induced adverse effects, assuming that significantly less oxycodone would be administered compared to morphine. Finally, equivalent doses were administered in the first 24 hours. Also, this is the first study showing that choosing i.v. oxycodone for pain relief without a dose reduction strategy does not appear to be beneficial compared to morphine. This result is ultimately in line with previous studies which have shown that the occurrence of opioid-related side effects is primarily related to the total dose administered. Using morphine doses of $45 \mu\text{g kg}^{-1}$ or oxycodone $30 \mu\text{g kg}^{-1}$ as i.v. bolus, Silvasti et al. found no difference within the first 24 hours after breast surgery on a weak collective (50 patients) [19]. Performing plasma assays, these authors demonstrated that morphine and oxycodone appeared to be equipotent as described in our study.

With less dose of oxycodone compared to morphine (respectively, 13 ± 10 mg vs 22 ± 10 mg, $p < 0.001$) after hysterectomy under general anesthesia, Lenz et al demonstrate a lower total rate of adverse events in favour of oxycodone, but there were no significant differences in the incidence of nausea, vomiting, or itching [22]. For these authors, their results support the findings in experimental studies in humans, demonstrating that oxycodone is more potent than morphine in the treatment of visceral pain [22]. After laparoscopic supracervical hysterectomy, Kim et al. compared i.v. oxycodone to fentanyl (ratio 1:75) and found that the amount of PCA during the first 48 hours after surgery was significantly less in group oxycodone than in group fentanyl group. However, rate of nausea (48% vs 14% in fentanyl group), vomiting, dizziness and drowsiness occurred significantly more often in group oxycodone within the first postoperative 48 hours [29]. Conversely, no significant difference between the 2 groups were noted for ORAEs in a similar study [28]. Finally, in our study including hip arthroplasty, both groups ultimately received equivalent doses and similar incidence ORAEs occurred (Table 2, 3). These results corroborate the latest meta-analyze performed in oncology [11–13].

Oxycodone Adverse Events And Pain Relief

The incidence of nausea, vomiting or sedation were similar between the two groups, < 10% (Table 3). For NVPO, the rate appeared to be low but probably related to the systematic prevention of nausea used in this study. With oxycodone, the incidence of PONV in the literature vary according to dose-related studies and route of administration (p.o., i.v., s.c...) [15–19, 23]. In fact, no study appears to ultimately demonstrate superiority to oxycodone versus morphine. Urinary retention was the most frequent ORAEs reported in PACU. This event may vary depending on the type of surgery and is largely linked to the duration of general anesthesia and intraoperative fluid administration. With similar characteristics in both groups (duration of surgery, intraoperative sufentanyl), the main reason for this lack of difference between groups was probably linked to the similarity of the adjustment dosing regimen between the two groups with close final doses in PACU.

With regard to acute postoperative pain during the first 48 hours postoperatively, oxycodone and morphine demonstrated similar NRS pain trajectory and satisfaction (Fig. 2) and no further conclusions can be drawn.

Titration

Studies conducted in major orthopedic surgery or comparing young patients with elderly patients have shown that i.v. morphine administration every 5 min with an unlimited number of 2- or 3-mg boluses provided the best and fastest analgesia [5, 6]. In the present study, we demonstrated that with a similar administration regimen, the morphine group tended to experience more pain in the PACU and required more adjustments ($p = 0.03$) (Table 3, Fig. 2). In fact, the difference between the groups for pain relief is summarized by the administration of a single additional dose of morphine. This small difference translates into a gain of only 5 minutes in favour of oxycodone in PACU. Moreover, the number of patients who had the full dose of maximal i.v. titration was similar between the two group. Is this really an argument in favour of its preferred use, given that the incidence of side effects remains the same? This question remains unanswered.

Limite Of The Study

The present study also had several limitations. First, this study included only arthroplasty surgery (intermediate pain). Also, different results could be noted with other surgeries and different selected populations (bias related to individual variations in psychological disorders or pain sensitivity). The incidence of pain and adjustment doses vary according to gender, age and type of surgery (anterior, posterolateral...). Our results are only valid for a relatively healthy patient population (not too old, not too fat, no kidney failure, no use of preoperative opioids) and for this procedure only. Second, this study was performed at two different centers, which may weaken the power of the data as many subtle issues (surgeons, anesthesiologists, everyday practice, patient recruitment), but intra and post-operative care

were standardized. Third, the ratio chosen 1/1 is always a source of discussion and disagreement between the experts due to peak effect (1/1, 1 / 1.5, 1/2) [30]. To reduce external bias, we decided to use a similarity of all volumes and doses with an extending evaluation within the first 24 hours. Composites (results) are often used to reduce sample size, but can cause particular problems when the components are of different importance to patients, occur with different frequencies and are affected to a different degree by the intervention. The high and similar frequency of ORAEs in our study corresponds to this ideal of choice. Finally, the fact that this study excluded opioid patients prior to surgery is an important nuance that has a substantial impact on the generalizability of the study, as many patients who underwent surgery for painful reasons are already receiving opioid treatment. Moreover, this study did not assess oxycodone upon discharge that should be evaluated.

Conclusion

In conclusion, for orthopaedic pain relief, i.v. oxycodone, administered at a morphine dose conversion ratio of 1:1, did not reduce ORAEs for the first 24 hours post-operatively and provided similar pain scores and satisfaction. This appears to demonstrate that oxycodone is not more potent than morphine in this indication.

Abbreviations

i.v.
intravenous
NRS
Numeric Rating Scale
ORAEs
Opioid-Related Adverse Events
PACU
Postoperative Care Unit
PCA
Patient Controlled Analgesia
RR
Respiratory Rate

Declarations

- Ethics approval and consent to participate: the present study was approved by the institutional human investigation committee (Comité de Protection des Personnes, CPP, Nîmes, France, EudraCT: 2011-004140-22, Chairperson Prof T. Lavabre-Bertrand) on 7 January 2012 and was registered before started on ClinicalTrials.gov (NCT 01536301). A written informed consent was obtained from all participants before inclusion.

- Consent for publication: not applicable
- Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- Competing interests: The authors declare that they have no competing interests
- Funding: this work was only supported by our institutional sources (Carémau Hospital, Nîmes, France) and funding were only used for the payment of IRB and to purchase study drugs.
- Authors' contributions: all authors have read, revised and approved the final manuscript. PC, MR and OL were responsible for the conception and design of the study, for the coordination of the centres and data analysis. PC and JYL wrote the manuscript. SA was responsible for data and statistical analysis. LZ, VR, CB, NV and JLH were responsible for the patient recruitment and for anesthetizing the patients.
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Tables

Due to technical limitations, Tables 1-3 are provided in the Supplementary Files section.

Figures

Figure 1

Flow diagram of the study

Figure 2

Box and whisker plots showing the median, interquartile range, and range of pain scores at rest (Fig2 A) and at movement (Fig2 B) across time for oxycodone and morphine group. Baseline was performed at inclusion (> 24h and < 6 weeks before surgery). PACUi: initial scores after extubation and before titration in Post Operative Care Unit. PACUd: scores at discharge. No difference was observed between groups at baseline.*< 0.05 vs oxycodone

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.docx](#)
- [Table3.docx](#)
- [CONSORTChecklist3.doc](#)
- [Table2.docx](#)