Reports of Original Investigations

Early oral analgesia after fast-track cardiac anesthesia

[L'analgésie orale précoce après la technique accélérée d'anesthésie cardiaque]

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Purpose: Oral analgesia after "fast-track" cardiac anesthesia has not been explored. The aim of this study was to compare two oral oxycodone analgesic regimens.

Methods: One hundred-twenty patients scheduled for coronary artery bypass grafting were randomly assigned postoperatively to receive immediate-release oxycodone 5 mg and acetaminophen 325 mg (Percocet-5) (group I) *per os* four times daily, or controlled-release oxycodone 10 mg (OxyContin) (group II) *per os* every 12 hr and placebo twice daily. Acetaminophen 500 mg *per os* was used as first-line rescue medication, and immediate-release oxycodone (syrup form) 5 mg *per os* as second-line rescue medication. Pain intensity was assessed with a visual analogue scale on the first postoperative day, the morning after extubation, and thereafter four times daily for four days. Use of rescue medication and adverse events were recorded.

Results: Baseline demographic and operation-related characteristics were similar in both groups. While pain control was good in both groups, the immediate-release group experienced less pain on all postoperative days ($P = 0.003$), required significantly less rescue medication, and had fewer adverse effects such as somnolence and nausea.

Conclusion: Peroral oxycodone is effective for early pain control after fast-track cardiac anesthesia. Immediate-release oxycodone/acetaminophen appears to provide better analgesia and fewer side effects compared to controlled-release oxycodone.

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Objectif *: L'analgésie orale après la technique accélérée d'anesthésie cardiaque n'a pas été étudiée. Le but de cette étude était de comparer deux régimes d'analgésie à l'oxycodone per os.*

Méthodes *: Cent-vingt patients devant subir une chirurgie de revascularisation myocardique ont été aléatoirement répartis en deux groupes après l'opération : le groupe I a reçu 5 mg d'oxycodone à libération immédiate et 325 mg d'acétaminophène (Percocet-5) per os quatre fois par jour, et le groupe II a reçu 10 mg d'oxycodone à libération contrôlée (OxyContin) per os chaque 12 h et un placebo deux fois par jour. L'acétaminophène (500 mg per os) a été utilisé comme médicament de sauvetage de première intention et l'oxycodone (5 mg per os à libération immédiate sous forme de sirop) comme médicament de sauvetage de seconde intention. L'intensité de la douleur a été évaluée à l'aide d'une échelle visuelle analogue le premier jour après l'opération, le matin suivant l'extubation, puis quatre fois par jour pendant quatre jours. L'utilisation de médicaments de sauvetage ainsi que les complications ont été enregistrées.*

Résultats *: Les caractéristiques démographiques de base ainsi que celles en rapport avec l'opération furent similaires dans les deux groupes. Bien que le contrôle de la douleur ait été bon dans les deux groupes, les patients du groupe à libération immédiate ont ressenti moins de douleur durant les jours suivant l'opération ($P = 0,003$), ont eu besoin d'une dose significativement moindre de médicaments de sauvetage, et ont subi moins d'événements négatifs tels que la somnolence ou la nausée.*

Conclusion *: L'oxycodone peroral est efficace pour un contrôle de la douleur précoce après une technique accélérée d'anesthésie cardiaque. L'oxycodone / acétaminophène à libération immédiate semble fournir une meilleure analgésie et moins d'effets secondaires que l'oxycodone à libération contrôlée.*

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PAIN after cardiac surgery may be caused by the sternotomy, leg vein harvesting, pericardiotomy, and chest tube insertion.[1,2] Opioids - specifically *iv* morphine - have been the mainstay of postoperative analgesia since the introduction of cardiac surgery. A potential alternative to *iv* morphine is oxycodone, a strong oral opioid agonist, used alone or in combination with mild analgesics. Oxycodone has an analgesic potency comparable to morphine[3] and is suitable for oral administration due to its high bioavailability (60%). Several studies in patients after noncardiac surgery reported good pain control and high patient satisfaction with rapid conversion of *iv* opioid analgesics to oral immediate-release or controlled-release oxycodone.[4–6]

A review of the recent literature[7] suggests that immediate-release and controlled-release oxycodone have similar efficacy in the treatment of noncancer pain and similar side effects. Controlled-release oxycodone may offer the advantage of less frequent dosing, thereby decreasing nursing workload. There is no difference in the bioavailability of these two formulations.

Immediate-release oxycodone is absorbed in a mono-exponential manner (time to maximum serum concentration, one hour; mean half-life by single-dose pharmacokinetics, 3.5–5.65 hr; mean time from administration to analgesia, 0.52 ± 0.33 hr) and controlled-release oxycodone in a bi-exponential manner (rapid phase with mean half-life of 0.52 hr accounting for 38% of the dose, followed by a slow phase with a mean half-life of 6.2 hr).[8]

In 2001, our department introduced a fast-track protocol for coronary artery bypass grafting (CABG), and peroral postoperative analgesia became part of routine practice. The aims of the present study were twofold: first, to investigate the safety and efficacy of early conversion from an *iv* to an oral opioid regimen after fast-track cardiac surgery; and secondly, to compare postoperative analgesia between immediate-release oxycodone/acetaminophen and controlled-release oxycodone. Our null hypothesis is the assumption that postoperative analgesia after use of immediate-release oxycodone/acetaminophen is not different from analgesia provided by controlled-release oxycodone.

Materials and methods

The study was conducted in a tertiary-care, university-affiliated centre using a double-blind, randomized, controlled design. The protocol was approved by our institutional review board, and all patients provided written informed consent on enrolment. The study group consisted of 120 patients scheduled for elective CABG between January and June 2003 and targeted for fast-track anesthesia with low-to-moderate-dose fentanyl, early extubation, early mobilization, and an intensive care unit (ICU) stay of less than 24 hr. Preoperatively, patients scheduled for an off-pump coronary artery bypass procedure were excluded from the study, as were patients with a history of chronic analgesia or tranquilizer use or dependence on alcohol. Patients with clinical malabsorption, renal insufficiency, or hepatic disorders (abnormal liver function) were also excluded. Postoperative exclusion criteria consisted of delayed transfer to the general ward (i.e., ICU stay > 24 hr) or readmission to the ICU. The following data were collected: preoperative - age, sex, body mass index, history of diabetes, and renal insufficiency; intraoperative - type of procedure, urgent or emergent operation, duration of anesthesia, and duration of cardiopulmonary bypass (CPB); ICU-related - duration of ventilation, ICU length of stay, score on the visual analogue scale (VAS), and need for inotropic support at the time of extubation.

All patients received a standard anesthesia protocol. Premedication consisted of midazolam syrup 0.1 $mg \cdot kg^{-1}$ *po*, and anesthesia was induced with fentanyl 10 to 15 $\mu g \cdot kg^{-1}$ *iv* and midazolam 0.02 to 0.04 $mg \cdot kg^{-1}$ *iv*. Pancuronium bromide was given to facilitate endotracheal intubation, and the lungs were then ventilated with an oxygen/air mixture to maintain normocapnia. Anesthesia was maintained with isoflurane, fentanyl, and midazolam. The total intraoperative dose of fentanyl was 30.1± 9.2 $\mu g \cdot kg^{-1}$ and of midazolam, 0.12 ± 0.09 $mg \cdot kg^{-1}$. All operations were carried out through a median sternotomy. The internal thoracic artery was used in all cases and was harvested in a skeletonized manner; the left radial artery and saphenous vein were used at the discretion of the surgeon and were harvested in an open technique. Anticoagulation was achieved with 3 to 4 $mg \cdot kg^{-1}$ of heparin to reach and maintain an activated clotting time > 480 sec. Standard CPB management included use of a membranous oxygenator, arterial line filters, nonpulsatile flow, and maintenance of mean arterial pressure above 60 mmHg. Myocardial protection was achieved by multiple administration of anterograde and/or retrograde blood cardioplegia. Topical cooling was not mandatory. Core temperature was decreased to approximately 30°C in almost all cases according to our department policy. All patients were rewarmed to 37°C before discontinuation of CPB. At the end of surgery, heparin was reversed with protamine. Patients were returned to the cardiothoracic ICU while still intubated.

Postoperative care consisted of mechanical ventilation in the assist-control mode, cardioactive drugs when indicated, and the use of warm air heaters to maintain normothermia. Analgesia was provided by intermittent *iv* morphine injections, and sedation, by intermittent *iv* midazolam injection to maintain a Ramsay sedation score of ≥ 3 during assisted ventilation. All medications were given by a nurse. Midazolam and morphine consumption were recorded. Criteria for weaning from the ventilator were hemodynamic stability (no use, or decreasing use of cardioactive drugs), absence of significant bleeding (≤ 100 $mL \cdot hr^{-1}$), absence of significant arrhythmias, adequate urine output (≥ 1 $mL \cdot kg^{-1} \cdot hr^{-1}$), and oxygen saturation > 95% with fractional concentration in inspired oxygen less than 0.50; patients also needed to be sufficiently awake to follow commands. Patients fulfilling these criteria were placed on pressure support ventilation of 8 cm H_2O for 20 to 30 min, and in the absence of respiratory or cardiac distress, extubation was performed immediately thereafter. Inotropic drug administration was continued when needed. According to our institutional protocol, based on the study of Ovrum,[9] the patient was seated in a chair 45–70 min after extubation followed by transfer to the ward three to five hours later, and was full mobilized ten to 12 hr later.

After extubation, patients were randomized in a double-blind manner into two groups of 60 each. Randomization was achieved by placing instructions for one of the two postoperative analgesia options in each of 120 envelopes. The envelopes were sealed, mixed and assigned a number from 1 to 120. Each patient was consecutively assigned one envelope, and medication was administered according to the instructions, in a ratio of 1:1. All medical and nursing staff, except one of the investigators (N.P.), was blinded to the results of randomization. Group I patients received immediate-release oxycodone 5 mg and acetaminophen 325 mg *per os* (Percocet-5, Taro Pharmaceuticals, Israel) four times daily, at 06:00 hr, 12:00 hr, 18:00 hr, and bedtime (± 1.5 hr each time, at least four hours following the previous dose). Group II patients received controlled-release oxycodone 10 mg *per os* (OxyContin, Rafa Laboratories, Israel) twice daily, at 06:00 hr and 18:00 hr, with matching placebo at 12:00 hr and bedtime. The first dose was given 30–60 min after tracheal extubation. Pain intensity was assessed at rest with the ten-point VAS scale.[10] Use of the scale was explained to the patients preoperatively. A difference of 1 in the VAS score corresponds to a 30–35% change in pain intensity after surgery, which may be considered a meaningful change, in accordance with previous studies.[11] Pain assessment was performed on the first postoperative day, the morning after extubation, 1.5 hr after the first analgesic medication, and thereafter four times daily (morning, afternoon, evening and overnight) for four days. Acetaminophen 500 mg *per os* served as the first-line rescue medication, and immediate-release oxycodone (OxyCode syrup) 5 mg *per os* as the second-line rescue medication.

Use of rescue medication and adverse events were recorded. Somnolence was defined as difficulty to arouse during the pain assessment interview. Vomiting was defined as one episode of vomiting during the study period. Nausea, pruritus, headache and dizziness were recorded. Renal dysfunction was defined as a rise in creatinine of > 0.5 $mg \cdot dL^{-1}$ after cardiac surgery. Stroke was defined as a new fixed neurological defect that persisted at least 24 hr after surgery. Postoperative atrial fibrillation was defined as the characteristic arrhythmia, lasting for at least 15 min and confirmed on 12-lead electrocardiogram, and occurring within the first four postoperative days.

Statistical analysis

After we conducted a pilot study to assess the VAS mean and standard deviation, a sample size calculation estimated that 60 patients in each group were required to achieve 84% power to detect a difference of 1 VAS score unit between groups, with estimated group standard deviations of 2.4 at a significance level (alpha) of 0.05.

Continuous data are expressed as mean (± SD) and categorical data as number (%). Differences between groups were analyzed with Student's *t* test, Chi-square or Fisher exact test, as appropriate. Repeated postoperative VAS measurements were analyzed by the repeated measures general linear model. A *P* value < than 0.05 was considered significant. The statistical analysis was performed with SPSS 13.0 for Windows.

Results

All of the 120 randomized patients completed the study protocol. No patients were excluded because of delayed transfer to general ward or ICU stay > 24 hr, or re-admission to ICU. There were no significant differences between the immediate- and controlled-release oxycodone groups with respect to preoperative, intraoperative, or postoperative variables (Tables I and II). Mean VAS scores were significantly higher in group II compared to group I ($P < 0.05$ for all assessment points) (Figure). On multivariate linear analysis with repeated measures, after adjustment for age, sex, use of bilateral thoracic arteries, diabetes,

TABLE I Patient Characteristics and Preoperative Medications

Characteristic	*Immediate-release oxycodone/acetaminophen (n = 60)*	*Controlled-release oxycodone (n = 60)*
Age (yr)*	65.5 ± 11.8	66.1 ± 11
Sex (female)	22	21
Weight (kg)*	72.3 ± 9.8	75.1 ± 8.8
NIDDM	57	51
COPD	4	7
Recent myocardial infarction	14	12
Unstable angina	41	37
Severe LV dysfunction	7	5
EuroSCORE*	5.2 ± 1.8	4.1 ± 2.1
ASA II/III	4/56	5/55
Preoperative antiplatelet medication	60	60
Preoperative β-blockers	35	38

NIDDM = non-insulin-dependent diabetes mellitus; COPD = chronic obstructive pulmonary disease; LV = left ventricular; EuroSCORE = European System for Cardiac Operative Risk Evaluation; ASA = American Society of Anesthesiologists. *Values are mean ± SD. All other values are numbers of patients.

TABLE II Intraoperative data and postoperative outcomes

Characteristic	*Immediate-release oxycodone/acetaminophen (n = 60)*	*Controlled-release oxycodone (n = 60)*	*P value*
Internal mammary artery used	60	60	
Double internal mammary artery used	3	4	0.76
Number of anastomoses*	3.2 ± 0.8	3.3 ± 0.8	0.34
Anesthesia time (min)*	348 ± 49.8	324.4 ± 59.6	0.11
Total fentanyl consumption ($\mu g \cdot kg^{-1}$)*	28.9 ± 10.5	31.1 ± 8.4	0.23
Intraoperative midazolam consumption ($mg \cdot kg^{-1}$)*	0.11 ± 0.08	0.12 ± 0.09	0.34
Postoperative midazolam consumption ($mg \cdot kg^{-1}$)*	0.12 ± 0.04	0.11 ± 0.05	0.12
Total midazolam consumption ($mg \cdot kg^{-1}$)*	0.23 ± 0.07	0.23 ± 0.08	0.78
Total morphine consumption (mg)*	8.8 ± 5.1	9.5 ± 5.6	0.09
Ventilation time (hr)*	6.9 ± 2.5	7.8 ± 2.4	0.1
ICU LOS (hr)*	13.5 ± 4.2	14.7 ± 3.4	0.11
Hospital LOS (days)*	4.5 ± 1.8	4.1 ± 1.3	0.3

ICU = intensive care unit; LOS = length of stay. *Values are mean ± SD. All other values are number of patients.

chronic obstructive pulmonary disease, renal failure, congestive heart failure and low left ventricular function, only the type of analgesia remained a strong independent predictor of VAS score ($P = 0.003$).

More patients in group II required rescue analgesic medication at all time points (Table III), and more had adverse events (12/60, or 20% *vs* 7/60, 11.7% in group I) (Table IV). The most frequent adverse event was somnolence, occurring in seven patients (11.7%) in group II and two patients (3.3%) in group I ($P < 0.01$), followed by nausea in six patients (10%) and five patients (8.3%), respectively. No cases of impaired liver function were observed in either group. There were no analgesia-related or other complications that warranted readmission to the ICU.

Discussion

The key findings from this study disprove our null hypothesis, and demonstrate that immediate-release oxycodone/acetaminophen provides superior analgesia compared to controlled-release oxycodone.

Studies have shown that fast-track management is becoming common practice in many cardiac surgical departments, increasing bed turnover[12] and decreasing resource utilization[13] at no extra risk to patients.[14] The rapid postoperative rehabilitation procedure that is mandatory for the success of fast-track management (early ambulation after tracheal extubation, followed by transfer to the ward within several hours and full mobilization on the same day)[9] requires optimal pain management. For fast-tracking, administration of opioids, the mainstay of postoperative analgesia, via the standard *iv* or patient-controlled route[15,16]

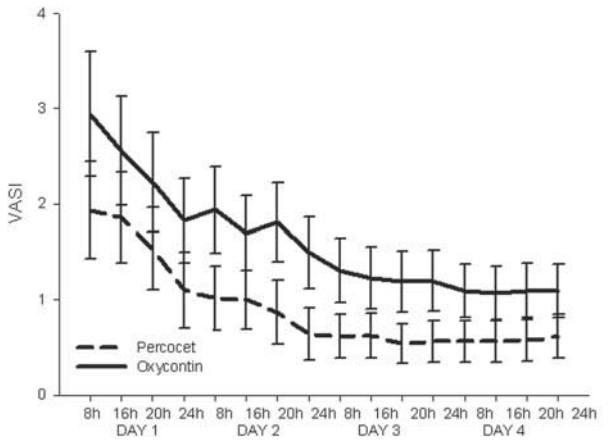

FIGURE Visual analogue scale scores in patients receiving immediate-release (Percocet) or controlled-release oxycodone (Oxycontin) for four days after fast-track cardiac surgery. Data are presented as means ± 95% confidence limits. Mean scores were higher in the controlled-release group ($P < 0.05$) at all assessment points.

is unfeasible. Once patients are able to tolerate oral medications, the oral route is preferred, because it is more convenient, noninvasive, and less expensive.[17] Combined oral and rectal administration on the first postoperative day is also reliable,[18,19] although some patients find the latter route of drug administration distressing.

Balanced or multimodal analgesia involves the selective use of specific drugs in combination. The concept relies on using multiple analgesic drugs with different modes of action (for example non-opioids combined with an opioid) There is now good evidence that this approach improves analgesia due to additive or synergistic effects, permitting the doses of the individual drugs to be reduced, thereby reducing the incidence and severity of adverse effects.[20] The administration of non-opioid oral agents for postoperative pain would avoid the respiratory depression and drowsiness associated with opioids, but the limited analgesia makes them useful only as adjuncts. Legeby *et al.*[21] reported that after breast surgery the addition of non-steroidal anti-inflammatory drugs (NSAIDs) to paracetamol and opioid-PCA reduced opioid consumption and improved pain relief at rest, but not convincingly during mobilization. Postoperative blood loss was also higher with diclofenac. Bainbridge *et al.*[22] suggested that in patients less than 70 yr of age undergoing cardiothoracic surgery, the adjunctive use of NSAIDs with narcotic analgesia reduces 24-hr VAS pain scores and narcotic requirements. Fayaz *et al.*[23] suggested that diclofenac alone or with paracetamol has a significant opioid-sparing effect after CABG, allowing for earlier extubation and improved oxygenation. Accordingly, Hynninen *et al.*[18] and Kulik *et al.*[24] suggested that NSAIDs not be used as monotherapy. Nonopioid analgesics, which include acetaminophen, aspirin, NSAIDs, and cyclooxygenase-2-specific inhibitors (coxibs), are frequently used for analgesia. Although all of these agents are effective at controlling pain, inhibition of prostaglandins (PGs) by NSAIDs may result in untoward cardio-renal effects, including hypertension, fluid and electrolyte abnormalities, congestive heart failure, acute renal failure, and nephrotic syndrome. Because acetaminophen has a different mechanism of action from conventional NSAIDs, it does not inhibit peripheral PGs at recommended dosing, and therefore appears to have a more favourable cardiovascular and gastrointestinal safety profile.[25] Cyclooxygenase-2 inhibitors, such as paracoxib and valdecoxib were associated with an increased incidence of cardiovascular events after CABG, arousing serious concern regarding their use in this setting.[26,27] Berger *et al.*[28] reported that oral acetaminophen (paracetamol) was well absorbed in the early period after cardiac surgery. In our study, patients who received Percocet (oxyco-

TABLE III Use of rescue analgesia in patients receiving oral analgesia after fast-track cardiac surgery

Postoperative day	*Immediate release oxycodone/acetaminophen*		*Controlled release oxycodone*		*P value*	
	Acetaminophen	*Oxycodone syrup*	*Acetaminophen*	*Oxycodone syrup*	*Acetaminophen*	*Oxycodone syrup*
Day 1	10	6	18	11	0.05	0.01
Day 2	5	2	7	4	0.05	0.01
Day 3	2	1	4	3	0.05	0.01
Day 4	2	0	4	2	0.05	0.01

Values are number of patients.

TABLE IV Adverse events in 120 patients receiving oral analgesia after fast-track cardiac surgery

Adverse event	*Patients (n)*				
	Immediate-release oxycodone/acetaminophen		*Controlled-release oxycodone*		*P value*
Somnolence	2	(3.3%)	7	(11.7%)	0.01
Nausea	14	(23.3%)	16	(26.7%)	0.52
Pruritus	2	(3.3%)	2	(3.3%)	NS
Vomiting	2	(3.3%)	3	(5%)	0.31
Dizziness	1	(1.67%)	1	(1.67%)	
Headache	1	(1.67%)	0		
Atrial fibrillation	12	(20%)	11	(18.3%)	0.26
Renal dysfunction	2	(3.3%)	2	(3.3%)	
Stroke	1	(1.67%)	0		

done/acetaminophen) had better analgesia compared to patients who received oxycodone only. However, Lahtinen *et al.*[29] suggested that *iv* propacetamol did not enhance analgesia, nor did it decrease cumulative opioid consumption or reduce adverse effects for three days after surgery.

Although Frenette[30] emphasized that potent opioid analgesia can be administered orally, there are limited data on the conversion dosing from *iv* to oral opioids after fast-track cardiac surgery. The present study showed that the early conversion was well tolerated. Regarding the type of oral regimen, Reuben *et al.*,[31] in a comparison of immediate- and controlled-release oxycodone after outpatient orthopedic surgery, found that a controlled-release regimen provides better analgesia. However, many orthopedic procedures are associated with more intense postoperative pain than cardiac surgery. In contrast, Gammaitoni *et al.*[32] compared controlled-release oxycodone with immediate-release oxycodone/acetaminophen (Percocet) in patients after oral surgery and found the immediate-release agent to be superior. Our study also demonstrates better results with immediate release of a combination of opioid and acetaminophen than with controlled release of opioid alone following fast-track cardiac surgery.

We observed that the commonly reported opioid side effects[6,31–34] were present with both regimens, namely, somnolence, dizziness, pruritus, nausea and vomiting. Respiratory depression, one of the most concerning side effects of opioid medications, was not observed in either group, nor were there any acetaminophen-related side effects, including hepatotoxicity. Overall, the incidence of side effects was lower in our study than previously reported, and the frequency of side effects was less in the immediate- than the controlled-release group.

The present study has several limitations. First, the anesthetic technique was not tightly controlled, and included different doses of fentanyl intraoperatively and morphine postoperatively. Second, we compared immediate-release oxycodone/acetaminophen with controlled-release oxycodone without acetaminophen. Third, only a single dosage and a single duration of treatment were assessed. Fourth, our inclusion of only low-risk patients with a EuroSCORE of 4–5, limits interpretation of the findings for higher-risk cardiac surgery populations.

In conclusion, this randomized, double-blind trial demonstrates that oral oxycodone effectively controls postoperative pain after cardiac surgery. The combination of immediate-release oxycodone/acetaminophen (Percocet) was associated with significantly better analgesia compared to controlled-release oxycodone, with fewer adverse effects. We suggest that the analgesia provided by the combined regimen provides an additive effect, allowing improved analgesia with smaller doses of each drug, thereby limiting side effects associated with each class of analgesic medication. Further studies are warranted to corroborate and expand these findings.

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