J Anesth (2014) 28:580–586
DOI 10.1007/s00540-013-1770-x

ORIGINAL ARTICLE

A randomised trial of oral versus intravenous opioids for treatment of pain after cardiac surgery

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Received: 30 September 2013 / Accepted: 6 December 2013 / Published online: 28 December 2013

Abstract
Background Cardiac surgery and sternotomy are procedures accompanied by substantial postoperative pain which is challenging to treat. In general, intravenous (IV) opioids are used in the immediate postoperative phase, followed by oral opioids. Oral opioids are easier to use and generally less expensive. Our goal was thus to determine whether a new opioid preparation provides adequate analgesia after sternotomy. In particular, we tested the primary hypothesis that total opioid use (in morphine equivalents) is not greater with oral opioid compared with patient-controlled IV morphine. Our secondary hypothesis was that analgesic efficacy is similar with oral and IV opioids.
Methods A total of 51 patients having elective cardiac surgery were enrolled in this study. After rapid postoperative respiratory weaning, the patients were randomised into one of two groups receiving different types of analgesia: oral Targin (a combination of oxycodone–hydrochloride and the opioid antagonist naloxone hydrochloride-dihydrate) or patient-controlled IV morphine. Pain score (visual analogue scale), sedation (Ramsey score), respiratory rate and side effects were assessed at 3, 5, 7, 9 and 11 h after surgery, and every 6 h throughout the third postoperative evening.
Results The total opioid dose in morphine equivalent doses was significantly lower with oral opioid than with IV morphine (adjusted geometric means [95 % confidence interval]: 34 [29; 38] vs. 69 [61; 78] mg, respectively). Pain scores were similar in each group.
Conclusions Analgesic quality was comparable with oral and IV opioids, suggesting that postoperative pain even after very painful procedures can be sufficiently managed with oral opioids.

Keywords Anaesthesia · Opioid · Pain · Surgery

This study was registered at clinicaltrials.gov (NCT01816581).

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Introduction

Skin incisions, intraoperative tissue retraction and dissection, intravasal cannulations and drainages, sternotomy and pericardiotomy all contribute to intense pain after cardiac surgery [1, 2]. As might be expected, the treatment of such pain remains challenging [1]. Poorly controlled thoracic pain may contribute directly or indirectly to postoperative complications, including myocardial ischaemia, hypoventilation and atelectasis, delayed return of gastrointestinal function and decreased mobility [2, 3]. There is also a strong association between prolonged acute pain and subsequent development of persistent incisional pain [4].

Opioids are the most commonly used medications for the treatment of acute severe postoperative pain, and their analgesic efficacy is undisputed. Opioids are usually given intravenously during the initial postoperative days and then continued orally. Patient-controlled analgesia (PCA) is widely used and effective [4], but requires trained staff and expensive equipment [5].

Once patients tolerate oral medications, oral administration is preferred because it is convenient, non-invasive, easier and generally less expensive [2]. Early postoperative administration of oral opioids would therefore facilitate analgesic management and presumably reduce healthcare costs. The aim of our study was to determine whether a oral opioid preparation, Targin (a combination of oxycodone hydrochloride and the opioid antagonist naloxone hydrochloride dihydrate), provides postoperative analgesia comparable to that provided by IV PCA. In particular, we tested the primary hypothesis that total opioid use (in morphine equivalents) is smaller with oral opioid compared with PCA IV morphine.

Methods

This study is registered at clinicaltrials.gov (NCT01816581) and was conducted in the Department of Cardiothoracic and Vascular Anaesthesia and Intensive Care Medicine at the Medical University of Vienna. With approval from the Ethics Committee of the Medical University Vienna and after obtaining written informed consent from prospective patients, we enrolled 51 patients scheduled for elective conventional on-pump cardiac surgery requiring a median sternotomy between July 2011 and May 2012.

Patients were randomly allocated to one of two treatment arms: postoperative oral opioid (oral group) or IV PCA morphine (PCA group). Targin is a controlled-release oral medication that consists of a fixed ratio of two drugs per tablet: the opioid oxycodone hydrochloride (20 mg) and the opioid antagonist naloxone hydrochloride dihydrate (10 mg). Oxycodone is a potent semi-synthetic opioid analgesic that has been in clinical use since 1917 for the treatment of severe pain [6]. It is effective in severe chronic pain, whether nociceptive, cancer-related or neuropathic pain [7]. Naloxone is a potent μ-receptor antagonist.

All patients had American Society of Anesthesiologists (ASA) physical status scores of 3 or 4, were aged 18–90 years and were expected to be extubated within 4 postoperative hours. Exclusion criteria were chronic use of opioids, tranquilizers or pain medications within 3 months; hypersensitivity to opioids; use of monoamine oxidase inhibitors in the 2 weeks before surgery; alcohol or drug abuse; renal dysfunction (glomerular filtration rate of <30 ml/min/1.73 m^2 or need for dialysis); liver dysfunction defined as Child–Pugh Score 7–15; ejection fraction of <40 %; malabsorption syndrome; neurologic or cognitive dysfunction; pregnancy; severe respiratory depression; severe chronic obstructive pulmonary disease; severe bronchial asthma; non-opioid induced paralytic ileus; history of seizures.

Based on our observations in recent years at the Medical University of Vienna, we noted that patients recovering from sternotomy required about 50 ± 15 (standard deviation, SD) mg IV morphine sulphate during the first 3 postoperative days. We thus estimated that 72 patients would provide 80 % power at an alpha level of 5 % based on a 20 % treatment effect. Because cardiac surgery is a difficult study setting and there was thus substantial potential for patients dropping out, our aim was to enrol 100 patients.

Protocol

Patients were premedicated with up to 7.5 mg midazolam. General anaesthesia was induced with fentanyl at approximately 3 μg/kg, propofol at approximately 1.5 mg/kg and rocuronium at approximately 0.6 mg/kg. General anaesthesia was maintained with sevoflurane combined with 0.2–0.4 μg/kg/min remifentanil as clinically necessary. At 30 min before the anticipated end of surgery, patients were given 1 g paracetamol intravenously. At the end of surgery, patients were transferred to the intensive care unit (ICU), still intubated and ventilated, and remifentanil was reduced to 0.05 μg/kg/min. Remifentanil was discontinued 3 h after surgery. Patients were thereafter given 1 g paracetamol intravenously at 6-h intervals throughout the first 3 postoperative days.

Using a "fast track" approach, patients were weaned from mechanical ventilation and extubated as quickly as possible. At 2 h after extubation, patients were tested for the ability to swallow. Patients were only randomised if swallowing was successful, and the swallowing test was assigned time zero. Randomisation (1:1) without stratification was based on computer-generated codes that were kept in sequentially numbered opaque envelopes.

Patients assigned to the PCA group were given a basal rate of 0.3 mg morphine per hour. The demand dose was a 1 mg bolus with a 5-min lockout, but no other hourly limit. Patients assigned to the oral group were given 20 mg Targin tablets at 12-h intervals, corresponding to a daily dose of 36 mg oxycodone. On their demand or when visual analogue scores (see below) exceeded 30 mm, patients were given an additional 5 mg oxycodone hydrochloride, which was repeated as necessary at 30-min intervals.

Measurements

Patients were instructed on the use of the visual analogue scale (VAS) for measuring pain and on the PCA pump the day before surgery. The VAS was evaluated using a slide rule which ranged from 0 mm (no pain) to 100 mm (worst pain) [8, 9]. Three hours after extubation, patients rated their pain using the VAS. We simultaneously recorded impairment of consciousness using the Ramsay Sedation Scale [10], spontaneous respiratory rate and potential side effects, including nausea, vomiting, anorexia, dizziness, headache and itching. The VAS, Ramsey sedation score [10], spontaneous respiratory rate, time of first defecation and potential side effects were also assessed at 3, 5, 7, 9, and 11 h after end of surgery. The same measurements were also made every 6 h throughout the third postoperative evening.

Statistical analysis

All postoperative opioid administrations were converted to IV morphine equivalent doses, with 20 mg of Targin being considered equivalent to 18 mg oral oxycodone and, therefore, to 9 mg of IV morphine [11–15].

Although the assignment of patients to the oral or PCA group was random, the risk of chance imbalance on potential confounding variables nonetheless existed due to the relatively small sample size of our study. We thus initially compared the randomised groups with respect to balance on baseline and intraoperative characteristics. Balance was assessed using standard univariable summary statistics as well as standardised difference scores [24]. The standardised difference score is an index that measures the magnitude of difference between groups on baseline variables; it is calculated as the difference in means, mean rankings or proportions divided by a common measure of standard deviation across the two groups. Any baseline or intraoperative characteristic displaying imbalance as characterised by a standardised difference of >0.1 in absolute value was considered for adjustment in all analyses comparing randomised groups.

To evaluate the primary hypothesis comparing the randomised groups on total IV morphine equivalent dose, we developed a linear regression model in which we applied the logarithmic transformation to morphine equivalent doses prior to modelling in order to model percentage differences between groups. Any imbalanced baseline variables (as per the criterion above) were considered for entry into the model; backward stepwise variable selection, with a selection criteria set conservatively at $P < 0.30$, was used to obtain the final multivariable model. The Wald test for regression model coefficients was employed to test for significance of treatment effect with Type I error rate set at 5 %.

To study the effect of oral opiate medication on pain score we used a linear mixed model [16]. This model allows for estimation of mean pain scores as a function of postoperative time while adjusting confidence interval (CI) estimates to accommodate for the correlation present among repeated pain measurements obtained from a given patient (we used a spatial power correlation structure, which assumes a greater degree of correlation among pain score measurements close together in time than among measurements distant in time from one another). Similarly, a linear mixed model was used to compare two randomised groups based on the rate of spontaneous breathing.

Regarding the impairment of consciousness in the Ramsay sedation scale, we only observed levels I, II and III during all postoperative days with 63 % of the times detecting level II and 36 % of the times detecting level III. To assess the level of sedation in the exploratory groups we transformed data into a binary variable (i.e. sedation score of III vs. I/II). We then used a logistic mixed model with adjustment for the correlation among repeated measures as for pain scores.

Likely complications (nausea, vomiting, anorexia, dizziness, headache and itching) were summarised into a collapsed composite binary outcome (i.e. any vs. none). The odds of experiencing one or more complications were compared between oral and control groups using logistic regression analysis (adjusting for the same factors as in the primary analysis). Incidence of each individual complication and constipation difficulties were also reported for each group.

Wald tests for regression model coefficients were used for each of the secondary hypotheses; the Bonferroni correction was applied in order to control the overall Type I error rate at 5 % for these secondary hypothesis tests [17]. R statistical software version 2.15.2 for the 64-bit Unix operating system (The R Foundation for Statistical Computing, Vienna, Austria) was used for all analysis (Fig. 1).

Results

The study enrolment was discontinued after 51 patients when the principal investigator (KR) moved from the University of Vienna to the University of Zurich. One of the 51 patients requested exclusion from the study 54 h after randomisation to the oral opioid group because of subjective discomfort. Thus, a total of 50 patients were included in the analysis, of whom 24 were given oral opioids and 26 were given IV opioids.

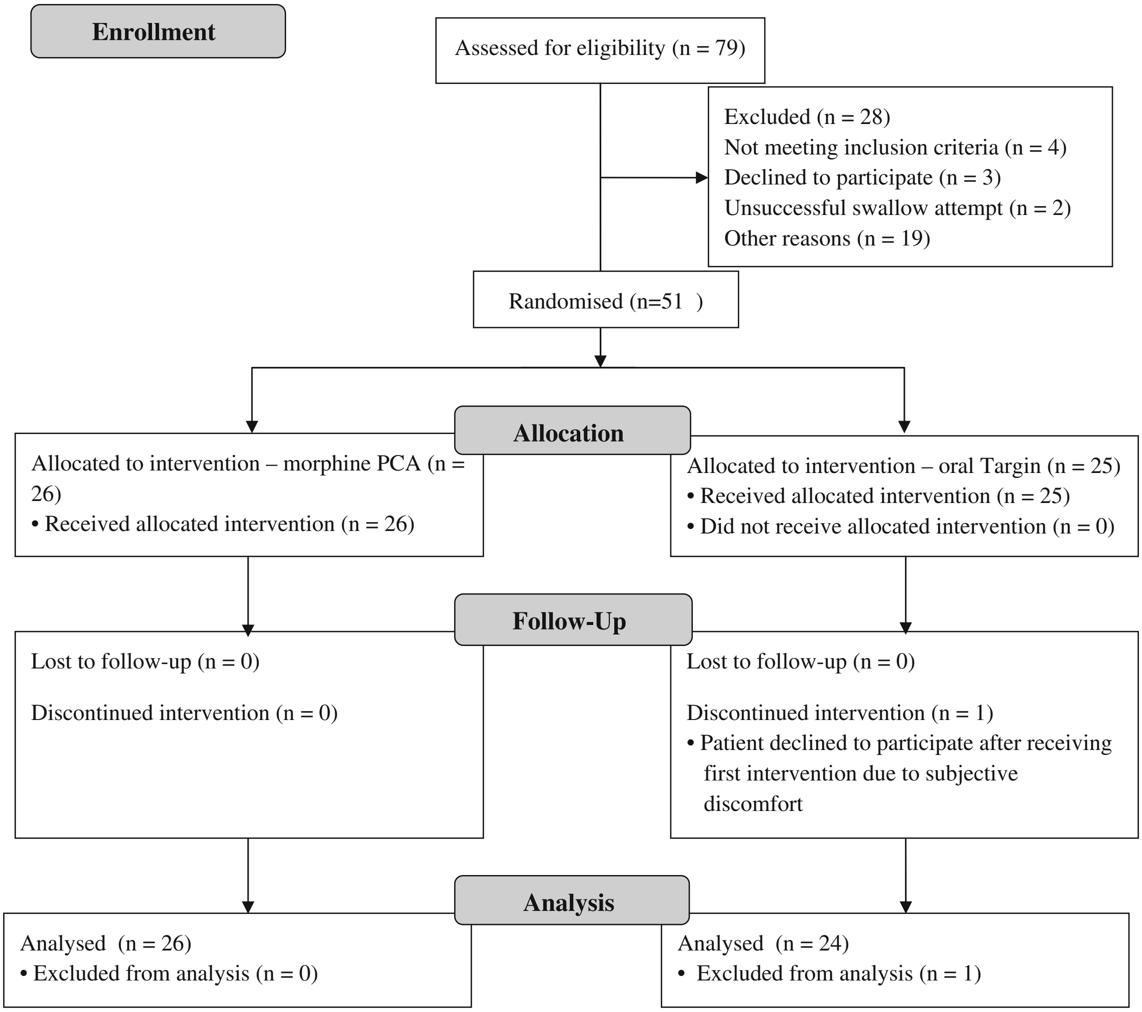

Fig. 1 Consort flow chart

Baseline and intraoperative characteristics of the two study groups are shown in Table 1. Patients randomised to oral group, by chance, were slightly older, more likely to be female, had a lower ASA physical status, had a lower body mass index (BMI), underwent shorter surgery and were mechanically ventilated slightly longer. We thus adjusted for these factors in all analyses.

Outcome variables are summarised in Table 2. As for the primary outcome, backward stepwise variable selection led to a final multivariable model with the following baseline potential confounding variables: age, BMI, type of surgery and duration of surgery. Adjusting for these variables, we found that the total IV morphine equivalent dose was significantly lower for oral group than PCA group (Wald test $P < 0.001$). That adjusted geometric mean [95 % CI] morphine equivalent doses were 34 [29; 38] mg and 69 [61; 78] mg for the oral and IV groups, respectively, and the corresponding ratio [95 % CI] of geometric means was 0.49 [0.41; 0.58]. The unadjusted observed median [1st quartile; 3rd quartile] morphine equivalent doses were 32 [29; 34] and 84 [45; 95] mg for the oral and IV groups, respectively.

Adjusted VAS pain score estimates as a function of postoperative time for each group are shown in Fig. 2. As shown on this figure, estimates appeared to be slightly higher in the oral group than in the PCA group. However, we found no significant time-dependence of the treatment effect in our sample (group–time interaction F test $P = 0.99$) and found no overall treatment effect of oral opioids after removal of the group–time interaction (adjusted difference in mean VAS pain scores [98.7 % CI] of 3.4 [−4.3, 11.2] points comparing the oral group to the PCA group; Wald test $P = 0.37$, using a significance criterion of 0.05/4 = 0.0125; Table 2). Adjusted mean [98.7 % confidence interval] VAS pain scores were 18 [13, 22] points and 14 [10, 18] points for the oral and IV groups, respectively; the unadjusted observed time-weighed mean [98.7 % confidence interval] pain scores were 17 [0, 44] and 14 [0, 41] points for the oral and IV groups.

Table 1 Summary of baseline and intraoperative patient characteristics

Factor	Intravenous group ($N = 26$)[a]	Oral group ($N = 24$)[a]	Standardised difference score
Female gender (vs. male)[b]	4 (15.4)	6 (25)	0.24
Age (years)[b]	63 ± 14	67 ± 15	0.27
American Society of Anesthesiologists' physical status[b]			
II	8 (30.8)	4 (16.7)	0.34
III	18 (69.2)	20 (83.3)	
Height (cm)	173 ± 9	170 ± 6	−0.42
Weight (kg)	85 ± 14	79 ± 12	−0.46
Body mass index (kg/m^2)[b]	28 ± 3	27 ± 4	−0.27
Type of surgery[b]			
Bypass	16 (61.5)	15 (62.5)	−0.02
Valve	10 (38.5)	9 (37.5)	
Duration of surgery (h)[b]	4.6 ± 0.9	4.3 ± 0.7	−0.36
Duration of anesthesia (h)[b]	6.1 ± 1.1	5.9 ± 0.9	−0.19
Duration of ventilation (h)[b]	12.2 ± 3.8	13.4 ± 3.8	0.33

Data are presented as the mean ± standard deviation (SD), or as the number (*N*) with the percentage in parenthesis, as appropriate

[a] Patients randomised to the "oral group" received postoperative oral opioid (Targin tablets); patients randomised to the "Intravenous group" received patient-controlled analgesia as intravenous (IV) morphine

[b] These factors were used for adjustment in our main analysis

Table 2 Major outcomes

Outcome	Comparison (oral vs. intravenous)	Estimate [95 % CI][a]	P[b]
Primary outcome			
Opioid equivalent dose	Adjusted ratio of geometric means	0.49 [0.41; 0.58]	<0.001
Secondary outcome			
VAS Pain Score	Adjusted difference of means	3.44 [−4.29; 11.17]	0.37
Ramsay sedation scale level	Adjusted odds ratio	0.95 [0.45; 1.99]	0.85
Spontaneous breathing rate	Adjusted difference of means	0.17 [−1.89; 2.22]	0.79
Side effects[c]	Adjusted odds ratio	0.27 [0.05; 1.48]	0.06

CI Confidence interval

Data are presented as oral vs. intravenous, adjusted for age, body mass index, type of surgery and duration of surgery using either linear regression (wherever differences in means or ratio of geometric means are reported) or logistic regression (wherever odds ratios are reported)

[a] Confidence limits for the secondary hypotheses reflect the Bonferroni adjustment for multiple comparisons in order to maintain an overall 5 % Type I error rate

[b] *P* is from the Wald tests of regression coefficients. Significance criterion of 0.05 for primary outcome and 0.05/4 = 0.0125 for the secondary outcomes

[c] Side effects is a composite binary outcome equal to "yes" if any of the following were present: nausea, vomiting, anorexia, dizziness, headache and itching

For the other secondary outcomes (Table 2), we found no significant group effect on either the spontaneous respiratory rate or the likelihood of being deeply sedated after covariate adjustment (Wald test $P = 0.79$ and $P = 0.85$, respectively). Likewise, the odds of side effects did not differ significantly (adjusted odds ratio [98.7 % confidence interval] comparing oral to IV groups: 0.27 [0.05; 1.48]; Wald test $P = 0.06$). The side effects are summarised in Table 3. For the given sample, patients given oral opioids had fewer side effects except for vomiting. The observed median length of ICU stay [1st quartile, 3rd quartile] was 1 [1, 2] days for both groups, while hospital duration was 8.5 [8, 12] days for the oral group and 9 [8, 11] days for the PCA group.

Discussion

Cardiac surgery with median sternotomy provokes considerable postoperative pain. Our results indicate that the administration of oral opioids provided comparable analgesia to IV PCA, while actually reducing overall opioid dose in morphine equivalents. Although our study was not powered for differences in side effects, based on our results, it appears that reduced opioid dose with oral administration may also reduce opioid-induced complications.

The oral administration of controlled-released tablets is not generally recommended during the initial postoperative day because of concerns about delayed drug absorption in the presence of decreased gastric emptying

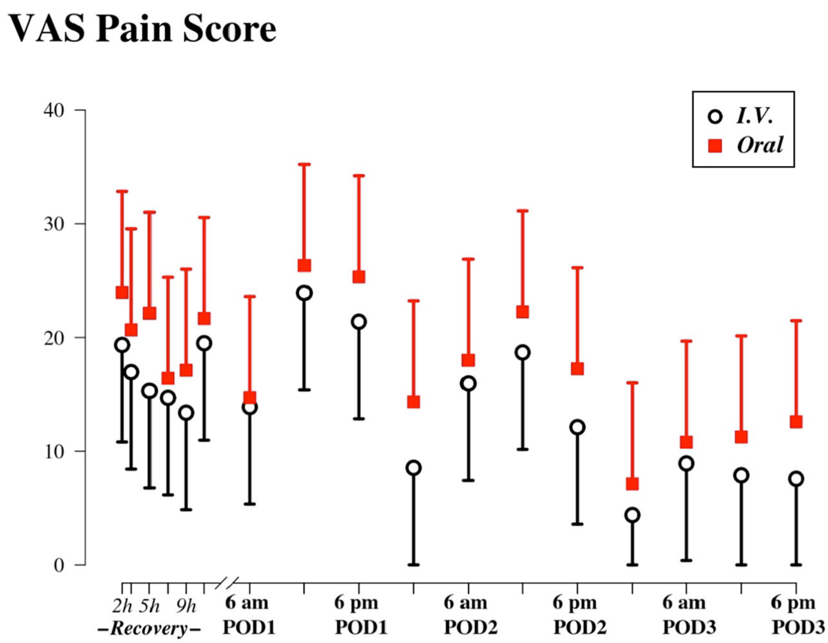

Fig. 2 Estimated mean visual analogue score (*VAS*) for pain for each of the randomised groups [*I.V.* intravenous group receiving IV morphine, *Oral* group receiving postoperative oral opioid (Targin tablets)] as a function of postoperative time. Recovery time is expressed as hours after extubation. *6 am POD 1*, *6 pm POD 1* The 06:00 am and 06:00 pm of the first postoperative day, respectively, *POD2* second postoperative day, *POD3* third postoperative day. *Error bars* extend to two standard errors (SE) of the mean (SE estimated via the respective linear mixed model). *Error bars below 0* were truncated. No group–time interaction was found for the pain score (*F* test $P = 0.99$), although estimates displayed come from the model with interaction. Estimates are adjusted for age, body mass index, type of surgery and duration of surgery

Table 3 Incidence of complications

Complication	Intravenous group ($N = 26$)	Oral group ($N = 24$)
Nausea	8 (31)	3 (12)
Vomiting	3 (12)	5 (21)
Anorexia	8 (31)	4 (17)
Dizziness	11 (42)	6 (25)
Headache	5 (19)	1 (4)
Itching	1 (4)	1 (4)
First Defecation (days, 0 = none during study period)		
0	15 (58)	11 (46)
1	0 (0)	2 (8)
2	2 (8)	4 (17)
3	9 (35)	7 (29)

Data are presented as the number of patients with the percentage in parenthesis

[18, 19]. Based on the results of their study, Valtola et al. [20] concluded that the absorption of oral drugs is low within the first 48 h after cardiac surgery. However, we found oral administration to be effective, which is consistent with other studies in patients undergoing non-cardiac operations [5, 21]. For example, Duellman et al. [22] reported that multimodal, pre-emptive analgesia, including oxycodone, is associated with lower opioid consumption and shorter hospitalisation after orthopaedic surgery. Similarly, Rothwell et al. [5] reported that oral analgesics were comparable to intravenous morphine after total hip replacement.

A common complication of opioids is paralytic ileus which can occur with either oral or intravenous administration [2]. Ileus, however, is most common after gastrointestinal surgery—especially after colon resection. We did not observe ileus in any of our patients, suggesting that the complication is relatively rare in cardiac patients. The incidence of opioid-induced respiratory and haemodynamic effects depends on the definition, the route of administration and the specific opioid given [23]. However, Ramsey sedation scores and spontaneous respiratory rates were comparable in both of our study groups.

The major limitation of our study is its low power for detecting clinically important effects of oral opioid administration on complications, a limitation that was worsened when the study was stopped for administrative reasons after only half the planned enrolment. Furthermore, the study was not double-blinded for organisational and administrative reasons. It is thus possible that the opioid administration route influenced patients' subjective responses, including pain perception. However, to the extent that pain perception was biased by administration route, one might expect that most patients would consider intravenous treatment to be more potent.

In summary, this is the first randomised trial of exclusive oral versus IV opioids for treatment of pain after sternotomy. The analgesic quality was comparable with each approach, suggesting that oral opioids can be sufficient even after very painful procedures and at an early stage after surgery.

Acknowledgments We thank the nursing team of the ICU 13B for their enthusiastic support.

Conflict of interest Funded by internal sources only. None of the authors has any personal financial interest in this research.

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