

Original Article

A comparison of sufentanil vs. remifentanil in fast-track cardiac surgery patients*

W. Z. A. Zakhary,¹ E. W. Turton,¹ A. Flo Forner,¹ K. von Aspern,² M. A. Borger³ and J. K. Ender⁴

1 Senior Consultant, 4 Head, Department of Anaesthesiology and Intensive Care Medicine, 2 Senior Registrar, 3 Head, University Department for Cardiac Surgery, Heart Center Leipzig, Leipzig, Germany

Summary

We retrospectively compared patients receiving remifentanil with patients receiving sufentanil undergoing fast-track cardiac surgery. After 1:1 propensity score matching there were 609 patients in each group. The sufentanil group had a significantly longer mean (SD) ventilation time compared with the remifentanil group; 122 (59) vs. 80 (44) min, $p < 0.001$ and longer mean (SD) length of stay in the recovery area; 277 (77) vs. 263 (78) min, $p = 0.002$. The sufentanil group had a lower mean (SD) visual analogue pain score than the remifentanil group; 1.5 (1.2) vs. 2.4 (1.5), $p < 0.001$ and consumed less mean (SD) piritramide (an opioid analgesic used in our hospital); 2.6 (4.7) vs. 18.9 (7.3) mg, $p < 0.001$. The results of our study show that although remifentanil was more effective in reducing time to tracheal extubation and length of stay in the recovery area, there was an increased requirement for postoperative analgesia when remifentanil was used.

Correspondence to: W. Z. A. Zakhary

Email: waseemzakariaaziz.zakhary@helios-gesundheit.de

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Introduction

Fast-track pathways have become an integral part of cardiac anaesthesia in order to allow for rapid tracheal extubation and to reduce intensive care unit length of stay, without affecting the quality of care [1]. It may lead to a more efficient use of resources especially if there is a shortage of intensive care unit (ICU) beds and increased demands by a more efficient use of resources [2]. It is popular due to its cost-effectiveness [3]. Different fast-track protocols have been developed for ICU or for specialised recovery areas. Fast-track pathways with the use of a recovery area [4] are effective in reducing time to tracheal extubation and ICU length of stay [1]. Although several studies have shown that the type of opioid plays a minor role in different fast-track protocols [5–7], it has been

difficult to compare studies due to the heterogeneity of fast-track protocols and differing definitions of fast-track success. The aim of this retrospective study was to compare the effects of remifentanil and sufentanil on a well-established fast-track pathway. The primary end-points were: mechanical ventilation time (i.e. time from arrival in the recovery area until tracheal extubation); length of stay in the recovery area; visual analogue pain scores; and piritramide (an opioid analgesic in common use in our institution) consumption on the day of operation. Secondary end-points were: length of stay in intermediate care; hospital length of stay; fast-track failure; in-hospital mortality; and postoperative complications such as postoperative nausea and vomiting, delirium and the incidence of tracheal re-intubation.

Methods

This retrospective observational study was performed in a single university-affiliated heart centre, was approved by the local research ethical committee and individual patient consent was waived. In the period from February to July 2017, we were obliged to change opioid management within our standard fast-track protocol due to the unavailability of remifentanil. During this period, we decided to use a continuous sufentanil infusion instead. We included all consecutive cardiac surgery patients admitted to the recovery area during this time period. This group was compared with an historical group of patients from the same time period the previous year (February–July 2016) who had received a continuous remifentanil infusion according to our standard fast-track protocol [4].

For all patients, anaesthesia induction was performed with fentanyl 200 µg and propofol 1–2 mg.kg⁻¹. A single dose of rocuronium or atracurium was used for neuromuscular blockade. For maintenance of anaesthesia, a continuous infusion of an opioid, in addition to sevoflurane 0.8–1.1% MAC during the pre-cardiopulmonary bypass period were used. During bypass, and until the end of the operation, a continuous propofol infusion 3 mg.kg⁻¹.h⁻² was used.

For patients in the sufentanil group, a continuous infusion of sufentanil was used during maintenance of anaesthesia: 1 µg.kg⁻¹.h⁻² until sternotomy; 0.5 µg.kg⁻¹.h⁻² until, and during, bypass; and 0.25 µg.kg⁻¹.h⁻² after weaning from bypass and until chest closure after which the infusion was stopped. The anaesthetist was allowed to give additional 10–20 µg boluses if deemed necessary. Sufentanil group patients were transferred with a propofol infusion 2 mg.kg⁻¹.h⁻² to the recovery area. For postoperative analgesia, intravenous metamizole 1 g was given before tracheal extubation. Boluses of intravenous piritramide 0.02–0.03 mg.kg⁻¹ could be given if necessary to achieve a target visual analogue pain score of < 4.

For patients in the remifentanil group, an uninterrupted continuous infusion of remifentanil 0.2–0.3 µg.kg⁻¹.min⁻² was used throughout the operation. During patient transfer from the operating theatre to the recovery area, anaesthesia was maintained with remifentanil 0.1–0.15 µg.kg⁻¹.min⁻² and propofol 2 mg.kg⁻¹.h⁻². Postoperative analgesia was commenced immediately after arrival in the recovery area as an intravenous bolus of piritramide 0.1 mg.kg⁻¹ and intravenous metamizole 1 g. Boluses of piritramide 0.02–0.03 mg.kg⁻¹ could be given if necessary to achieve a target visual analogue pain score of < 4.

At the end of the surgery, all patients had to fulfil the fast-track criteria. Patients were admitted to the recovery area if they were in a stable haemodynamic condition with a core temperature of at least 36 °C. Both the surgeon and the anaesthetist agreed to a fast-track pathway for each patient. The recovery area operated daily, Monday to Friday from 10:00 h to 22:30 h. It was managed by anaesthetists and nursing staff with a nurse-patient ratio of 1:3 and physician-patient ratio of 1:4.

Patients' tracheas were extubated when they fulfilled the extubation criteria (Table 1). Patient-controlled analgesia (PCA) was offered to patients with a high visual analogue pain score and high analgesic consumption, either in the recovery area or later in the intermediate care unit, according to the attending physician. All patients were

Table 1 Weaning, extubation and transfer criteria for patients undergoing fast-track anaesthesia.

Weaning criteria:

- Train-of-four (TOF) ratio > 0.9
- Pressure support ventilation; PS 10–12 cmH₂O, PEEP 0–5 cmH₂O, F_IO₂ ≤ 40%
- Arterial blood gases; PaO₂ ≥ 13.3 kPa, PaCO₂ ≤ 5.8 kPa
- Svo₂ ≥ 70%, serum lactate < 4 mmol.l⁻¹, no acidosis
- Chest drainage ≤ 200 ml in 1st h, ≤ 100 ml in 2nd h then ≤ 50 ml.h⁻¹

Criteria for tracheal extubation:

- Full consciousness, no neurological deficit
- Haemodynamically stable
- Core temperature ≥ 36 °C
- Arterial blood gases; PaO₂ ≥ 13.3 kPa, PaCO₂ ≤ 5.8 kPa with F_IO₂ 0.4
- Normal Svo₂
- Acceptable tidal volumes with pressure support of 8 cmH₂O and PEEP of 5 cmH₂O
- Blood loss < 100 ml.h⁻¹
- Normal serum lactate
- No new ECG or CXR changes

Criteria for transfer of patients from recovery area to IMC:

- Fully awake and alert with no neurological deficit
- Haemodynamic stability
- None, or minimal, inotropic support
- Arterial blood gases; PaO₂ > 12 kPa, PaCO₂ < 6.1 kPa, S_pO₂ > 96% breathing 2–6 l.min⁻¹ oxygen
- Urine output > 0.5 ml.kg⁻¹.h⁻²
- Blood loss < 50 ml.h⁻¹
- Normal serum lactate
- Normal Svo₂
- Cardiac enzymes and CXR warranting no further intervention
- Visual analogue pain score < 4

Svo₂, venous oxygen saturation; CXR, chest radiograph; IMC, intermediate care unit.

monitored for at least 2 h after tracheal extubation and were then transferred to the intermediate care unit once they fulfilled the transfer criteria (Table 1).

All patients received 4 mg dexamethasone following induction of anaesthesia as postoperative nausea and vomiting prophylaxis. Upon arrival in the recovery area, all female patients received 1.25 mg droperidol. Ondansetron 4 mg was added in patients with a history of postoperative nausea and vomiting. Postoperative delirium was scored before transfer using the nursing delirium screening scale (Nu-DESC), where ≥ 2 is considered positive. Patients transferred from the recovery area to the ICU (or directly back to the operating room), were considered fast-track failure patients.

For data collection, our clinical information system iMedOne® (Deutsche Telekom Healthcare and Security Solutions GmbH, Bonn, Germany) and our machine-readable patient's chart Medlinq® (Medlinq Softwaresysteme GmbH, Hamburg, Germany) were used. Data were imported to SPSS (SPSS® Statistics 22.0; Chicago, IL, USA) and StatsDirect (StatsDirect® version 3.0, StatsDirect Ltd, Cheshire, UK) for description and analysis. In order to minimise selection bias and to obtain comparable groups, a propensity score matching approach was used. For each patient, a logistic regression model was calculated that included variables known to affect postoperative lengths of stay. These included: age; sex; co-existing diseases; left ventricular ejection fraction; logistic European system for cardiac operative risk evaluation score (EuroSCORE); type and duration of surgery; and bypass and aortic cross-clamp times. Pairs were matched 1:1 with their nearest neighbour according to the closest propensity score of each subject. Based on the pre-matching range of baseline variable differences, the maximum caliper width for pair-matching was defined at 0.125 of the pooled logit score standard deviation. Categorical data were compared using the χ^2 -test or

Fisher's exact test where appropriate. Continuous variables were assessed for normal distribution using the Shapiro–Wilks test and data were compared using Student's t-test or Wilcoxon–Mann–Whitney test where appropriate. A p value < 0.05 was considered statistically significant.

Results

There were 622 patients in the sufentanil group and 679 patients in the remifentanil group. Eighty-three patients were excluded during the 1:1 propensity score matching process, resulting in two equal groups, each containing 609 patients (Fig. 1). Baseline characteristics and operative data for patients included in the study are shown in Table 2.

Ventilation time (i.e. time from arrival in the recovery area until tracheal extubation) and recovery length of stay were significantly longer in the sufentanil group compared with the remifentanil group (Figs. 2 and 3). Hospital length of stay was significantly longer in the remifentanil group compared with the sufentanil group. There were no differences between the groups in terms of intermediate care unit length of stay (Table 3).

Postoperative analgesia (piritamide) requirement during recovery area stay was significantly higher for patients in the remifentanil group compared with those in the sufentanil group. There was no difference in PCA requirement between the groups either during their stay in the recovery area or afterwards during their remaining hospital stay. The mean (SD) visual analogue pain score at the end of recovery area stay was significantly lower in the sufentanil group compared with the remifentanil group (Table 3). Mean sufentanil consumption was $0.969 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-2}$, with a mean (SD) total consumption of $3.100 (0.100) \mu\text{g}\cdot\text{kg}^{-1}$. There was no correlation between total sufentanil consumption and ventilation time ($r = 0.174$). There were no differences between the groups in terms of postoperative complications (Table 4).

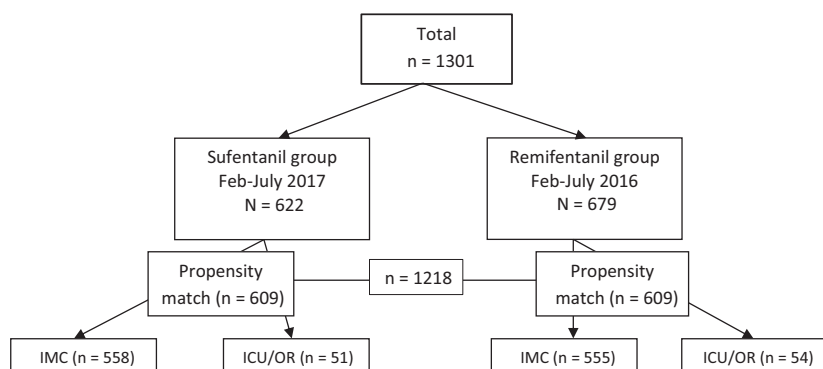
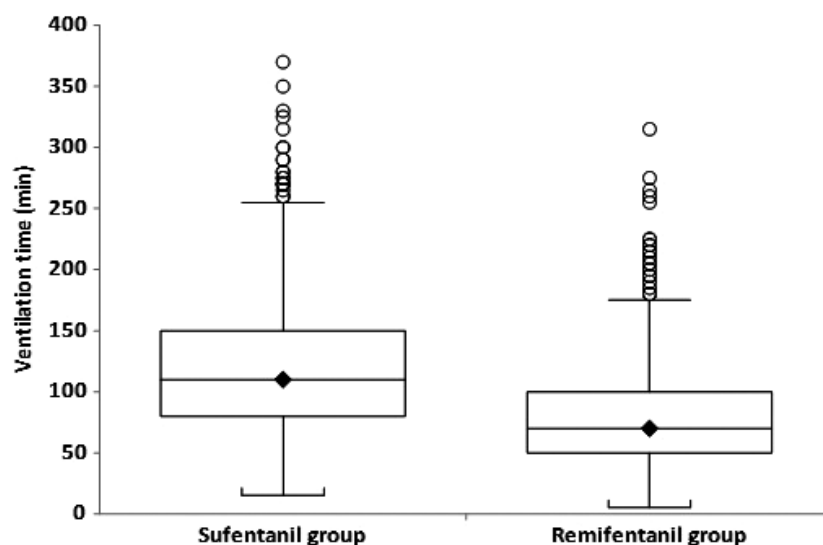


Figure 1 Study flowchart for patients included in the study. IMC, intermediate care unit; ICU, intensive care unit; OR, operating room

Table 2 Baseline characteristics and operative data for patients included in the study. Values are mean (SD) or number (proportion).

	Sufentanil group n = 609	Remifentanil group n = 609	p value
Age; years	65 (10)	65 (12)	
Sex; female	170 (27.9%)	145 (23.8%)	
Logistic EuroSCORE	5.1 (6.0)	5.6 (6.3)	0.096
Pre-operative ejection fraction; %	56.1 (10.3)	56.6 (10.5)	0.325
Pre-operative myocardial infarction	133 (21.8%)	142 (23.3%)	0.548
Pre-operative diabetes mellitus	197 (32.3%)	187 (30.7%)	0.528
Pre-operative COPD	32 (5.2%)	36 (5.9%)	0.623
Pre-operative serum creatinine; $\mu\text{mol.l}^{-1}$	88.1 (36.8)	90.7 (51.7)	0.315
Pre-operative neurological disorder	68 (11.1%)	72 (11.8%)	0.727
Urgent surgery	49 (8.0%)	57 (9.3%)	0.422
Aortic cross-clamp time; min	53 (36)	54 (37)	0.409
Cardiopulmonary bypass time; min	73 (48)	75 (49)	0.509
Operative time; min	193 (57)	190 (62)	0.411
Type of surgery:			0.923
CABG	149 (24.4%)	151 (24.7%)	0.947
OPCAB	142 (23.3%)	133 (21.8%)	0.583
1 × Valve replacement/repair	188 (30.8%)	193 (31.6%)	0.804
2 × Valve replacement/repair	14 (2.2%)	13 (2.1%)	0.999
3 × Valve replacement/repair	1 (0.2%)	2 (0.3%)	0.999
CABG+1 × Valve replacement/repair	58 (9.5%)	60 (9.8%)	0.922
CABG+2x Valve replacement/repair	1 (0.2%)	2 (0.3%)	0.999
CABG+ Others	5 (0.8%)	6 (1.0%)	0.999
Valve replacement/repair + Others	37 (6.0%)	36 (5.9%)	0.999
Miscellaneous	14 (2.2%)	13 (2.1%)	0.999

COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft; OPCAB, off-pump coronary artery bypass.

**Figure 2** A comparison of ventilation times between the sufentanil group and the remifentanil group. Horizontal line is median, boxes are IQR, lower whiskers are lowest range and upper whiskers are 1.5 upper IQR.

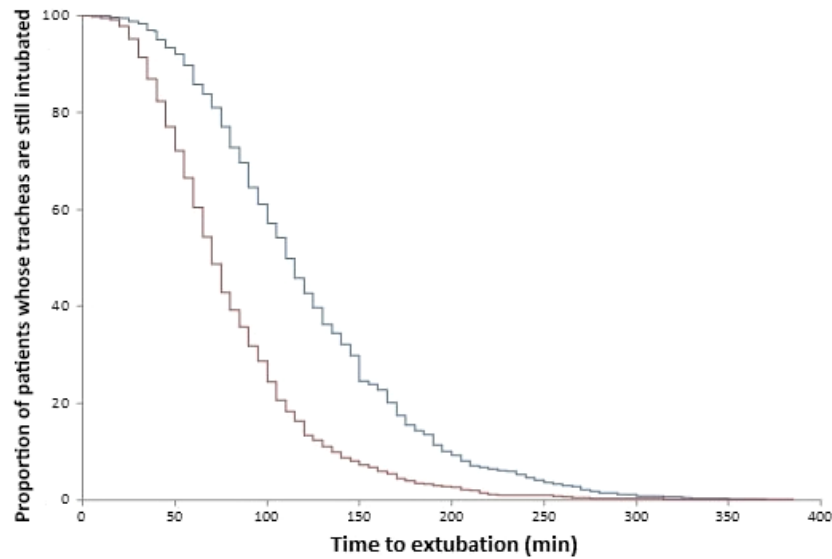


Figure 3 A comparison of the time to tracheal extubation between the sufentanil group (blue) and the remifentanil group (red).

Table 3 Postoperative outcome parameters for patients included in the study. Values are median (IQR [range]), mean (SD) or number (proportion).

	Sufentanil group	Remifentanil group	p value	95%CI of the difference
Ventilation time; min	110 (80–150 [15–370])	70 (50–100 [5–315])	<0.001	36.3 to 48.3
RA-LOS; min	277 (78)	263 (78)	0.002	5.09 to 22.6
IMC-LOS; h	65.1 (64.0)	68.7 (78.2)	0.364	–11.90 to 4.37
Hospital length of stay; d	14.1 (6.1)	15.5 (8.8)	0.020	–2.22 to –0.50
VAS pain score	1.5 (1.2)	2.4 (1.5)	<0.001	N/A
Piritramide requirement; mg	2.6 (4.7)	18.9 (7.3)	<0.001	–17.0 to –15.5
In- RA PCA requirement	11 (1.8%)	17 (2.7%)	0.339	N/A
Out- RA PCA requirement	62 (10.1%)	55 (9.0%)	0.559	N/A

RA, recovery area; IMC, intermediate care unit; LOS, length of stay; PCA, patient-controlled analgesia; VAS, visual analogue scale.

Table 4 Postoperative complications for patients included in the study. Values are number (proportion).

	Sufentanil group	Remifentanil group	p value
Fast-track failure	51 (8.3%)	54 (8.8%)	0.760
Tracheal re-intubation	3 (0.4%)	5 (0.8%)	0.725
Postoperative nausea and vomiting	95 (15.5%)	92 (15.1%)	0.873
Postoperative delirium (Nu-DESC \geq 2)	9 (1.8%) ^a	8 (2.4%) ^b	0.721
Deaths	1 (0.2%)	4 (0.6%)	0.374

Nu-DESC, nursing delirium screening scale.

^an = 483 ^bn = 321.

Discussion

We have demonstrated that a remifentanil infusion in cardiac surgery patients managed in a specialised recovery area using a fast-track protocol resulted in a significantly shorter ventilation time and length of stay in the recovery area compared with patients who received a sufentanil

infusion. However, the remifentanil group required more postoperative analgesia than the sufentanil group in order to reach the targeted visual analogue pain score. Remifentanil group patients had longer hospital stays, but there was no difference in intermediate care unit length of stay. There was no difference in fast-track failure rate,

tracheal re-intubation rate, in-hospital mortality, postoperative nausea and vomiting or incidence of early postoperative delirium.

In contrast to a recently published study [5], we demonstrated a reduction in ventilation time and recovery area length of stay with remifentanil. Bhavsar et al. did not demonstrate a difference between the two opioids; the ventilation time in their study was much longer, 311 vs. 80 min for the remifentanil group and 261 vs. 122 min for the sufentanil group. We found that the longer the ventilation time, the smaller the difference between groups (Fig. 3). The explanation for shorter ventilation times in our study might be differences in our fast-track protocol. Bhavsar et al. attempted awakening patients 1 h after their arrival in the cardiac recovery unit, whereas our weaning protocol started immediately after fulfilment of predefined weaning criteria. Another explanation might be the different opening hours of the recovery areas; in Bhavsar et al.'s study the opening hours were from Monday morning to Saturday afternoon, whereas our recovery area was closed overnight. Grass et al. [8] showed that limited opening hours led to decreased ventilation time. Differences in sufentanil dosages could be another explanation, however, we were unable to demonstrate a statistically significant correlation between total amount of sufentanil administered and ventilation time. This is in agreement with a study comparing different doses of sufentanil in fast-track patients which showed no difference in ventilation time [9]. Different studies have used comparable sufentanil dosages to ours but have reported much longer ventilation times. This supports our hypothesis that it is not the specific opioid, or the amount of opioid given, but the fast-track protocol itself that makes the difference [6, 10].

The increased requirement for postoperative analgesia in the form of piritramide in the remifentanil group is in agreement with previous studies [5, 6, 11]. This may be explained by the shorter context-sensitive half time of remifentanil (3–5 min) compared with sufentanil (30–35 min following a 4 h infusion). Visual analogue pain scores were significantly higher in the remifentanil group immediately postoperatively but were still within an acceptable range. Lison et al. [6] demonstrated similar differences in pain scores during the first hours of weaning, although Gerlach et al. [10] did not find any differences in repeated pain score measurements during the first 12 h postoperatively. In our study, the need for PCA due to high analgesic requirement caused by severe pain was comparable between the two groups, both during and after recovery area stay.

The sufentanil patients stayed longer in the recovery area before intermediate care unit transfer. Although this was statistically significant it is probably not clinically relevant; transfer of patients between different units is subject to logistical and administrative regulations that affect the time of transfer. Other studies have failed to demonstrate a difference in length of stay between the two groups [5, 6]. This can be explained by different fast-track pathways between studies (ICU vs. recovery area) and different opening hours.

Hospital length of stay was longer in the remifentanil group. This may be due to health system policy variance during the different time periods or due to less availability of step-down rehabilitation facilities during certain time periods. A Cochrane review on fast-track cardiac anaesthesia [1], indicated no difference in hospital length of stay, even in patients treated with high-dose opioids without a time-directed tracheal extubation protocol.

In our study, fast-track failure was defined as any unplanned transfer of the fast-track patient from recovery area directly to the ICU or a return to the operating theatre. There was a comparably low fast-track failure rate of 8% in both groups. This is in agreement with Lison et al. [6] who excluded approximately 10% patients in each of their groups due to failure in completion of the fast-track pathway. In contrast to Lison et al. [6], we did not find a high incidence of postoperative nausea and vomiting in our remifentanil group. This may be due to our postoperative nausea and vomiting prophylaxis strategy and a recent systematic review supports our results [11]. We did not find any differences between our groups in the incidence of postoperative delirium, assessed before transfer from the recovery area, suggesting that the type of opioid per se is not a risk factor for the development of postoperative delirium. This is in accordance with the findings of a prospective randomised study comparing the incidence of postoperative cognitive dysfunction (POCD) in cardiac surgical patients [12]. A ventilation time of more than 300 min, rather than the choice of opioid, was associated with POCD. This is in agreement with a recent study investigating causes of post-cardiac surgery delirium [13].

The main limitation of our study is its retrospective design resulting in a risk of potential bias. This is especially true for the significant difference in length of hospital stay between the two groups and may be the result of 'immortal time bias', that is, the concept that overall improvements in patient care occur more recently. An advantage of this study is the large number of patients included; it enabled us to detect even small differences in ventilation time.

In conclusion, although ventilation time and recovery area length of stay were shorter in the remifentanil group, sufentanil may be superior to remifentanil because it provided improved analgesia and resulted in a shorter hospital length of stay. However, we believe that a detailed and time-directed weaning protocol is more important than the use of a specific opioid for fast-track cardiac surgery patients.

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