A comparison of sufentanil versus remifentanil in fast-track cardiac surgery patients

Dissertation

zur

Erlangung des akademischen Grades

Doctor medicinae (Dr. med.)

an der Medizinischen Fakultät

der Universität Leipzig

Eingereicht von:

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Angefertigt an:

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Beschluss über die Verleihung des Doktorgrades vom: 17.12.2019

TABLE OF CONTENTS

1. List of abbreviations

6MWT	Six meter walk test
ABG	Arterial Blood gas
BIS	Bispectral index
CABG	Coronary artery bypass graft
COPD	Chronic obstructive pulmonary disease
CPB	Cardio-pulmonary bypass
CRA	Cardiac recovery area
CXR	Chest x-ray
EF	Ejection fraction
FT	Fast-track
FTCA	Fast-track cardiac anaesthesia
FTF	Fast-track failure
GA	General anaesthesia
IABP	Intra-aortic balloon pumping
ICU	Intensive care unit
IMC	Intermediate care unit
IQR	Interquartile range
LOS	Length of stay
LQ	Lower quartile
LV	Left ventricle
MAC	Minimum alveolar concentration
Nu-DESC	Nursing delirium screening scale
OR	Operation room
P.S.	Pressure support
PACU	Post anaesthesia care unit
PCA	Patient controlled analgesia
PCSU	Post cardiac surgery unit
POCD	Postoperative cognitive dysfunction
PONV	Postoperative nausea and vomiting

PSV	Pressure support ventilation
$Scvo_2$	Central venous oxygen Saturation
SD	Standard deviation
TEA	Thoracic epidural anaesthesia
TOF	Train-of-four
UQ	Upper quartile
VAS	Visual analogue score
V_T	Tidal volume

2. Bibliographic description:

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A comparison of sufentanil versus remifentanil in fast-track cardiac surgery patients

Universität Leipzig, Dissertation

46 Pages, 63 References, 8 Figures, 5 Tables.

3. Abstract:

A Fast-track pathway has become an integral part of cardiac anaesthesia. It enhances rapid extubation and reduces intensive care unit length of stay, without affecting the quality of care[1]. The Leipzig Fast-track protocol has been applied since 2005 and uses remifentanil continuous infusion as a main opioid for intraoperative maintenance of anaesthesia[2]. Remifentanil was unavailable in Germany from February to July 2017, therefore the protocol had to be modified and sufentanil was used instead.

In this study we retrospectively compared patients receiving remifentanil (February to July 2016) with patients receiving sufentanil (February to July 2017) undergoing fast-track cardiac surgery to evaluate differences between the two opioids concerning ventilation time (i.e. time from arrival on the post-anaesthesia care unit until tracheal extubation), length of stay in the post-anaesthesia care unit, visual analogue pain scores and piritramide consumption on the day of the operation.

Patients from the two time periods were matched using a propensity score matching resulting in 609 patients in each group. The remifentanil group had a significantly shorter median (IQR [range]) ventilation time compared with the sufentanil group; 70(50-100 [5-315]) vs 110 (80-150 [15-370]) min, p=<0.001, shorter mean (SD) length of stay in the post-anaesthesia care unit; 263 (78) vs 277 (77) min, p=0.002 and longer hospital length of stay 15.5(8.8) vs 14.1(6.1), p=0.02. The remifentanil group had a higher mean (SD) visual analogue pain score than the sufentanil group; 2.4 (1.5) vs 1.5 (1.2), p <0.001 and consumed more mean (SD) piritramide; 18.9 (7.3) vs 2.6 (4.7) 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 post-anaesthetic care unit, there was an increased requirement for piritramide with longer hospital length of stay when remifentanil was used.

4. Introduction:

4.1 Fast track cardiac anaesthesia:

4.1.1 Definitions:

Fast track (FT) surgery is a concept described by Kehlet and colleagues[3] for patients undergoing colonic surgery. It consists of proper integrated and interdisciplinary perioperative patient's management, which helps the patients' quick recovery and discharge from the hospital without affecting morbidity and mortality. Moreover, it reduces health care costs without increasing social burden. Staff training, patient education and procedures plans reorganization are all involved in fast-track surgery (Figure 1).

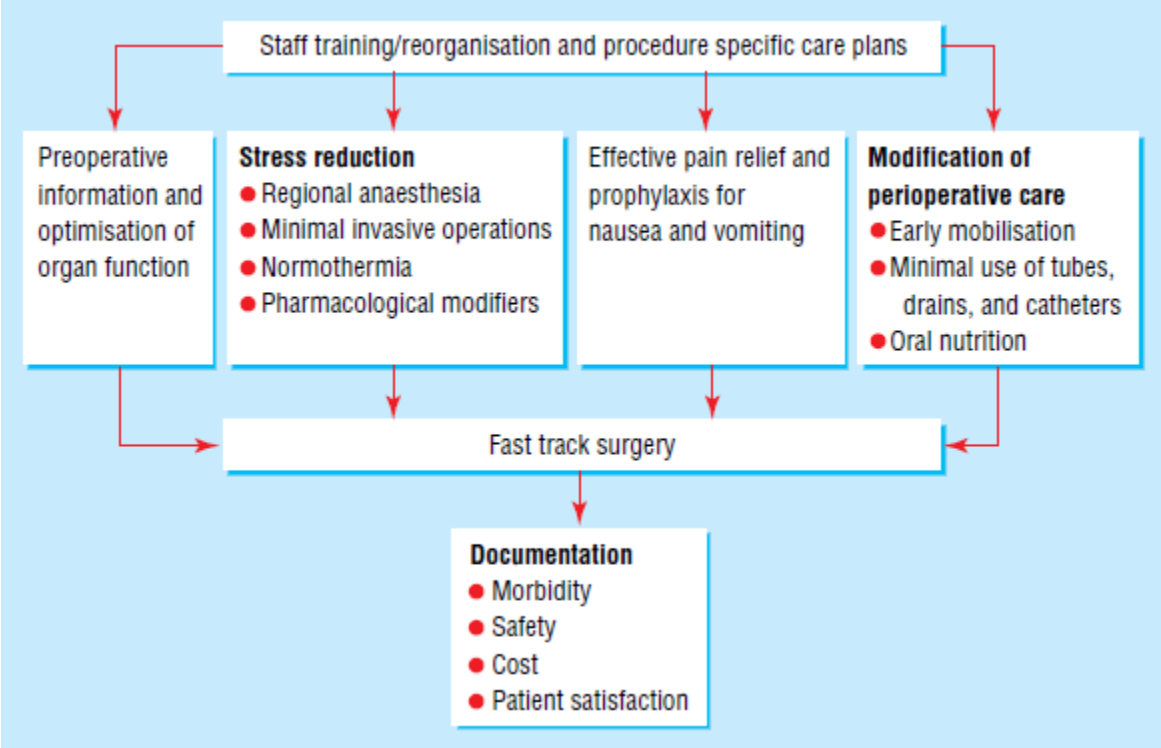


Figure 1: Interventions needed for major improvement in surgical outcome[3].

On the other hand, post-cardiac surgery care is a multidisciplinary process that uses multimodal managements to improve efficiency, patients' safety and use of resources.

Combing FT in post-cardiac surgery care resulted in what is called " Fast track cardiac anaesthesia" (FTCA), which was first introduced in the early 1990s[4].

For long time, cardiac surgery patients were given a high-dose opioid anaesthesia regime with long acting muscle relaxants to be ventilated overnight following their surgery. FTCA includes early extubation (<6hrs) leads to avoidance or short intensive care unit (ICU) stay and consequently early hospital discharge[5]. The imbalance between the demands and resources is the main motivation for evolution of such technique.

4.1.2 Current evidence of FTCA:

The mainstay of FTCA studies are; the safety of the technique, its efficiency and the costs benefits. The three topics were first discussed by the series of studies by Cheng et al. [6-8].

4.1.2.1 The safety of FTCA:

The safety of any new technique is usually tested by comparing its morbidity and mortality rate with the conventional high dose opioids based management as gold standard. Myles and colleagues[9] undergone a systematic review for six trials comparing mortality and morbidity for FTCA versus the conventional management and found no evidence of increase mortality and morbidity in FTCA patients. In a Cochrane review, comparing early extubation vs routine care, there was no significant difference in common complications such as reintubation rate, stroke and myocardial infarction as well as mortality rate during hospital length of stay (LOS), at 1 year or at any time during follow up[1]. Two other large studies could not find significant difference between both techniques [2, 10]. “Ultra-FT” is the term referred to immediate extubation in the operating theater and also found to be safe [11].

Moreover, in the same Cochrane review, they also compared FTCA with low dose to regular dose narcotic and found no differences in the risk of adverse events or mortality[1].

4.1.2.2 The efficiency of FTCA:

The effect of FTCA on reducing ventilation time (time to extubation), ICU- LOS, intermediate care (IMC)-LOS and hospital-LOS is well studied. The use of low-dose opioid anaesthesia and/or a time-directed extubation protocol is associated by reduction in time to extubation and in the ICU-LOS[1]. These two FT interventions are not associated with reduction of hospital-LOS[1]. This may attributed to organizational logistics and regulations that may hinder early hospital discharge for

suitable patients. To implement an effective FTCA pathway, the entire process of care must be modified, which is sometimes difficult. Modifications may include creation of step-down units that is separate from the ICU, modification to nursing coverage in ICU and using of telemetry monitoring[12].

Comparing quality of life is less investigated. Van Mastrigt [13] could show improvement in the physical and social functioning in FT patients at 1 month postoperatively. However, it was similar in both groups after 1 year.

4.1.2.3 Economic Implications of FTCA:

Most countries (including Germany) have increased the number of ICU beds to face increased demands [14, 15]. In Germany, the total ICU expenses consume about 20% of the overall hospital costs [16]. The most costly units after uncomplicated CABG are ICU and OR[7]. Moreover it was proved that, the first day of ICU admission has the highest impact on costs[17]. Therefore, FTCA have high impact on cost reduction by shortening or avoiding ICU admission[18]. In FTCA, the patients are transferred earlier to step-down units with lower nurse to patient ratio, leads to less staff expenses. Staffing represents 45-62% of total ICU costs[19]. The rest ICU costs are made up by supporting services (22-25%), supplies and equipment (15-20%) and drugs (4-13%)[19]. The implementation of specialized postoperative care unit (PACU), rather with limited opening hours[20], supports FT protocols implantation[21], increases safety and is cost effective[22].

4.1.3 Different FTCA pathways:

The primary driver for FTCA is cost reduction, which was difficult to be proved at the beginning of FT era. The evidences that FTCA reduces ICU LOS were weak, despite of reduction of postoperative ventilation time. This was hypothesized by incomplete switch of the hospital system to suit the FT idea[12]. Effective FTCA includes change of the entire process during surgery (e.g. maintain patient temperature, maneuvers to decrease postoperative bleeding) and postoperative pathways or model of care which has huge impact on cost.

Cheng et al.[23] had presented different postoperative pathway models for FTCA. Postoperatively, FT patients can be transferred either conventionally to common ICU, or to an ICU with special FT section (Integrated model) or to a separate postoperative care unit (PACU)

(Parallel model) or directly to step down unit if ultra-FT had been used (Figure 2). The flexibility in the staffing ratio according to the acuity of illness is the major advantage of these models and is the primary source of costs reduction. Probst el al. [21] compared FT in conventional model with that in PACU. The FT PACU patients were extubated faster (90 min. vs 478 min) and transferred to step down unit earlier (3.3 vs 17.9 hours).

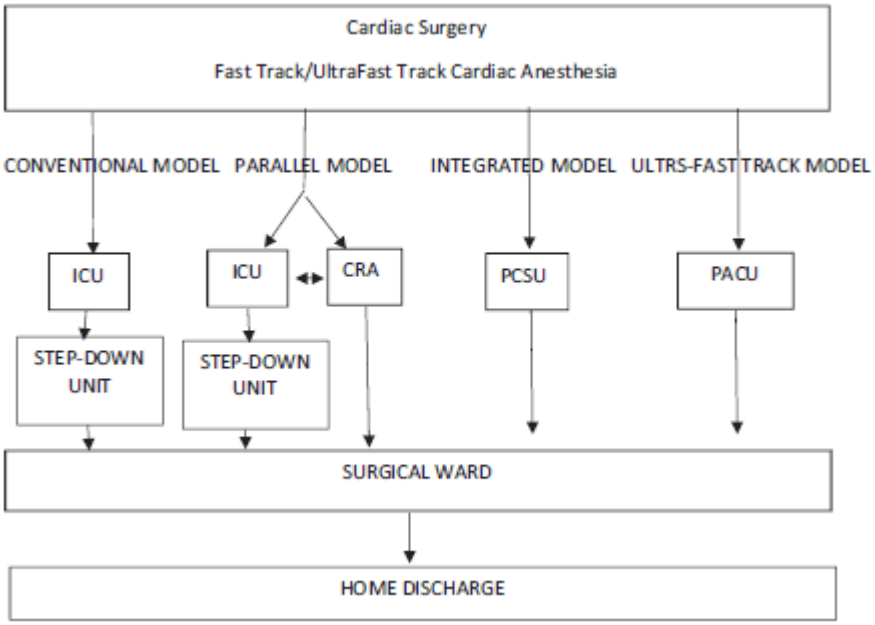


Figure 2: modified from [12, 24] Process of care.

ICU, intensive care unit; CRA, cardiac recovery area; PCSU, post cardiac surgery unit; PACU, post anaesthesia care unit

4.1.4 Patient selection and optimization:

Some authors suggested that, every patient could "basically" be suitable for FTCA.[25] However, literature showed FT failure (FTF) rates between 15.6% and 45.5%.[26, 27] Avoidance of risk factors that may lead to FTF or to prolonged ICU LOS, might be the best FTCA selection criteria[28]. Combined preoperative and intraoperative factors were been suggested to prolong ICU LOS independently. For example; age, chronic lung disease, high EuroScore [29], renal dysfunction, unstable angina, heart failure, re-do or combined surgery, prolonged

cardiopulmonary bypass (CPB)[30], transfusion more than four red blood cells (RBC) or plasma[31], sex, arrhythmias, mitral insufficiency, aortic surgery and intra-aortic balloon pumping(IABP)[32]. Furthermore, risk model were constructed to predict if the patient will have a prolonged ICU stay or not[32]. Prolonged ICU stay in cardiac surgery is related to postoperative mortality rate [33].

On the same way, risk factors and predictors for FTF were intensively examined [10, 26, 28, 34, 35]. Accordingly, some authors tried to construct a prediction model to predict FTF[26]. More recently, an operating room extubation prediction scoring system was validated by Subramaniam and coworkers[36]. Different studies have been used to stratify the patients into three groups of risk; low risk patients with higher success rate, medium risk and high risk with lower success rate (Figure 3)[28].

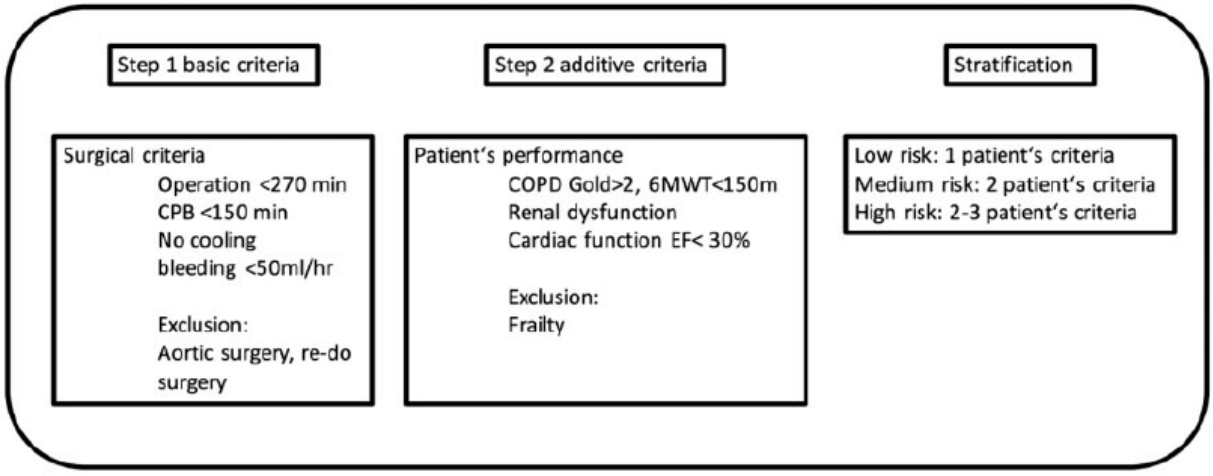


Figure 3: Recommended selection criteria and patient stratification[28].

CPB: Cardiopulmonary Bypass, COPD: Chronic obstructive pulmonary disease, 6MWT: Six meter walk test, EF: Ejection fraction.

Unfortunately, most of these factors are not modifiable (e.g. age, sex). However, patient optimizing strategies should focus on the modifiable factors. For example, protecting renal function can be reached by; keeping the hemodynamics stability, choice of fluids and reduce intravenous contrast media exposure short before surgery. Preoperative anemia and respiratory function can be modified in the same way.

FTF prediction and patient stratification are very useful for OR organization. Scheduling the FT patients first could be advantageous in keeping the FT program running well. Good communication and close cooperation between all the subjects involved in the patient care (e.g. OR manager, anesthesiologist, cardiac surgeon, cardiologist, perfusionist, nurses, intensivist…etc.) (heart-team approach) are fundamental for patient selection and optimization and finally a successful program.

4.1.5 Anaesthesia aspects of FT:

The previous standard of care in cardiac anaesthesia was based on high dose opioids (e.g morphine, fentanyl) and long-acting agents (e.g. midazolam, pancuronium) with postoperative sedation and mechanical ventilation for 6-24 hours. This protocol was largely shifted to short-acting agents enhancing early extubation. This was initiated by using propofol as a hypnotic agent (1-1.5mg/kg) or etomidate (0.2-0.3 mg/kg), reduced fentanyl dose (up to 15µg/kg) or using other novel opioids (e.g. remifentanil (0.2-0.5µg/kg/min), sufentanil(0.25-0.5µg/kg)) and short acting muscle relaxant as rocuronium 1mg/kg. Maintenance of anaesthesia may be achieved using continuous remifentanil/sufentanil infusion plus propofol or sevoflurane[37]. However, for successful FTCA, cardiac anesthesiologist has to do more than simple using of short-acting anaesthetics allowing early extubation and recovery. For example, depth of anaesthesia monitoring using derived cerebral electrical signals (e.g bispectral index (BIS) or Narcotrend) supports FT management. It can prevent inadequate anaesthesia in form of light anaesthesia and awareness or too deep anaesthesia and possible postoperative delirium especially in elderly patients [38, 39]. Good Intraoperative (and postoperative) temperature management is another prerequisite for successful FT. This can be achieved by practicing normothermic or mild hypothermic (> 32°C) cardiac surgery with standard application of forced-air or circulating-water devices and infusion warmer devices. Another challenge facing cardiac anesthesiologist is excessive bleeding prevention and management. Preoperative coagulation and antiplatelet optimization, intraoperative use of tranexamic acid, meticulous hemostasis and use of point-of-care (e.g. visco-elastic tests) for early diagnosis and directed-management could reduce postoperative bleeding and enhance successful FTCA.

Using thoracic epidural anaesthesia (TEA) as a supplementary measure in FT program is still point of debate. Its theoretical benefits of reducing intravenous opioids and better pain control with better ventilatory function[40] must be weighed against the possible epidural hematoma formation under systemic anticoagulation.

4.1.6 Cardiopulmonary bypass aspects of FT:

Many early postoperative complications (e.g. bleeding, respiratory and neurological complications), which hindered FT process, can occur during CBP period. In general, avoidance of CPB (e.g. off-pump coronary bypass or transcatheter valve implantation) is preferable. If CPB is a must, short CPB is preferable. Some measures must be taken to reduce complications rate. Severe hemodilution (hematocrit <24%) may lead to acute kidney injury[41]. It can be prevented by minimizing priming volume, ultrafiltration and vacuum-assisted venous return. Biocompatible CPB circuit and oxygenator are associated with shorter ICU LOS[42]. The use of "minimally invasive CPB" using close circuits with separation of shed blood from the surgical field, with or without the application of a reduced systemic anticoagulation [43], was shown to reduce postoperative complication [44].

4.2 Leipzig FT Protocol:

Leipzig FT protocol was first introduced in November 2005 for elective cardiac surgery patients in the heart center of Leipzig University. The primary main changes were switching of the opioid regime to remifentanil and the postoperative management in a specialized PACU, bypassing ICU admission [2, 22]. PACU consisted of 3 beds (upgraded to 8 beds on 2012) operated exclusively by anesthesiologists and anaesthesia nursing staff with a nurse to patient ratio of 1:3 and physician to patient ratio of 1:4. The PACU was operated daily Monday to Friday from 10:00am to 6:30pm. As of 2012 it is operated from 10:00am to 10:30pm. A 24hour operating time model was tested during the transitional period and was compared with 12hour model and found to be less effective[20].

Patients included in this protocol were preselected according to the preoperative medical condition and the planned surgery. Clinical judgment and communication between anesthesiologists and the surgeons at the end of the operation is mandatory. All patients were

admitted to the PACU (i.e. inclusion criteria) if they were hemodynamically stable, without or with minimal inotropic support, without excessive bleeding, and with a core temperature of at least 36°C. Only patients scheduled for elective cardiac surgery were admitted to the PACU. Elective surgeries include both elective and urgent (surgery performed on next working day) operations. Emergency surgeries (surgery performed immediately) were excluded. (Table 1)

Table 1: Inclusion Criteria for Fast Tracking

- Hemodynamically stable
- ± Low-dose inotropic support (continuous infusion of < 0.1µg/kg/min of norepinephrine and/or < 0.05 µg/kg/min of epinephrine or <5 µg/kg/min)
- No excessive bleeding
- Core temperature ≥36^{o}C
- Elective or urgent surgeries (not emergency surgeries)

Leipzig fast-track protocol consists of oral premedication with dipotassium clorazepate the evening before and midazolam on the day of surgery. Recently, preoperative oral premedication is omitted to reduce postoperative delirium rate[45] and to enhance fast extubation, except in rare cases. Anaesthetic induction is performed with propofol (1–2 mg/ kg), fentanyl (200µg), and rocuronium (0.6 mg / kg) or Atracurium (0.5 mg / kg). For maintenance of anaesthesia during the pre-cardiopulmonary bypass period, a continuous infusion of remifentanil (0.2-0.3 µg / kg / min) and sevoflurane (0.8– 1.1% minimum alveolar concentrations) is used. During and post-cardiopulmonary bypass, a continuous propofol infusion (3 mg /kg /h) is administered. A recruitment maneuver is carried out prior to weaning from cardiopulmonary bypass to prevent atelectasis. An external convective warming system with an underbody blanket (Bairhugger®; Arizant Healthcare, Eden Prairie, MN) is used after weaning from cardiopulmonary bypass to ensure a core temperature of 36°C. After surgery, patients are admitted to the PACU if they are in stable hemodynamic condition without (or with minimum) inotropic support and with a core temperature of at least 36°C. Only patients scheduled for elective cardiac surgery are admitted to the PACU. Postoperative analgesia consists of a bolus of piritramide (0.1 mg/kg) as required

and metamizole (1 g every 6 h) to achieve a pain score <4 on visual analogue score from 0 to 10 (0= no pain, 10= worst pain imaginable). Patients are extubated when they are fully awake, alert, hemodynamically stable, recovered full motor power (clinically and TOF>90%), without any neurological deficit, core temperature ≥36°C, acceptable blood gases on FiO_2 0.4, sufficient tidal volume (6-8 ml/kg) on minimal ventilator support (P.S. 8cmH_2O and PEEP 5cmH_2O) and normal lactate ,$ScvO_2$, ECG, CXR and without significant bleeding (<100ml/h chest tube drainage). Immediately after extubation, all patients undergo a noninvasive ventilation period of 0.5-1h.

All patients are sent to the intermediate care unit (IMC) if the following criteria are fulfilled: the patient must be awake, alert, no neurological deficit, pain score (VAS) <4, hemodynamically stable, without or minimal inotropic support with acceptable blood gas analysis (PaO_2 >90mmHg and $PaCO_2$ <46mmHg, SpO_2 >96% on O_2 flow 2-6L/min), no significant bleeding (< 50ml / h), urinary output >0.5ml/kg/h, normal serum lactate, normal $ScvO_2$, and when cardiac enzymes and chest x-ray warrants no further intervention. IMC patients are discharged to the nursing ward when they have stable rhythm and are able to mobilize independently. The weaning, extubation and transfer criteria are mentioned in table 2.

Table 2: Weaning, extubation and transfer criteria for patients undergoing fast track anaesthesia

Weaning Criteria:

- Neuromuscular Monitoring TOF> 90%
- Decrease the ventilator settings to PSV: PS 10-12 cm H_2O, PEEP 8-5 cm H_2O, f_iO_2 ≤40%
- Acceptable ABG: Pao_2 ≥100mmHg, $Paco_2$ ≤45mmHg (or Horowitz index ≥200 with a f_iO_2≤0.4)
- Normal ventilation mechanics
- Svo_2≥70%, s-Lactate < 4mmol.l^{-1} without acidosis
- No bleeding: Chest drainage ≤200ml in first hour, ≤100ml in second hour then ≤50ml.h^{-1}

Criteria for Extubation:

- Full consciousness, no neurologic deficit
- Hemodynamically stable
- Core temperature ≥36^{o}C
- Arterial blood gas: Pao_2 ≥100 mmHg, $Paco_2$ ≤44 mmHg on FIO_2 0.4
- Normal Svo_2
- Respiratory parameters: sufficient V_T (P.S. 8 cm H_2O and PEEP 5 cm H_2O)
- Bleeding: <100ml $.h^{-1}$
- Normal serum lactate
- No new ECG and CXR changes

Criteria for Transfer of Patients From PACU to IMC:

- Fully awake and alert, no neurologic deficit.
- Hemodynamically stable
- Without (or minimal) inotropic support
- Acceptable ABG (Pao_2>90 mmHg, $Paco_2$<46 mmHg, Spo_2 >96% on o_2 insufflation 2-6 L $.min^{-1}$)
- Urinary output >0.5 ml $.kg^{-1}.h^{-1}$
- No significant bleeding (<50 ml $.h^{-1}$)
- Normal serum lactate
- Normal $Scvo_2$
- Cardiac enzymes and CXR: warrants no further intervention
- VAS <4

TOF = Train-of-four, PSV= Pressure support ventilation, P.S. = Pressure support, $Scvo_2$ = Central venous oxygen Saturation, CXR=Chest x-ray, ABG= Arterial Blood gas, VAS= Visual analogue score, V_T = Tidal volume, IMC= Intermediate care unit.

4.3 Opioids:

The term “opioid” refers to all drugs, both synthetic and natural, that act on opioid receptors. They are the oldest analgesics known in the human history and its use in the practice of anaesthesia remains unchallenged[46]. They act through opioid receptors, which belong to the family of G protein-coupled receptors. The standard exogenous opioids used in OR are morphine, fentanyl, sufentanil, alfentanil and remifentanil (Figure 4).

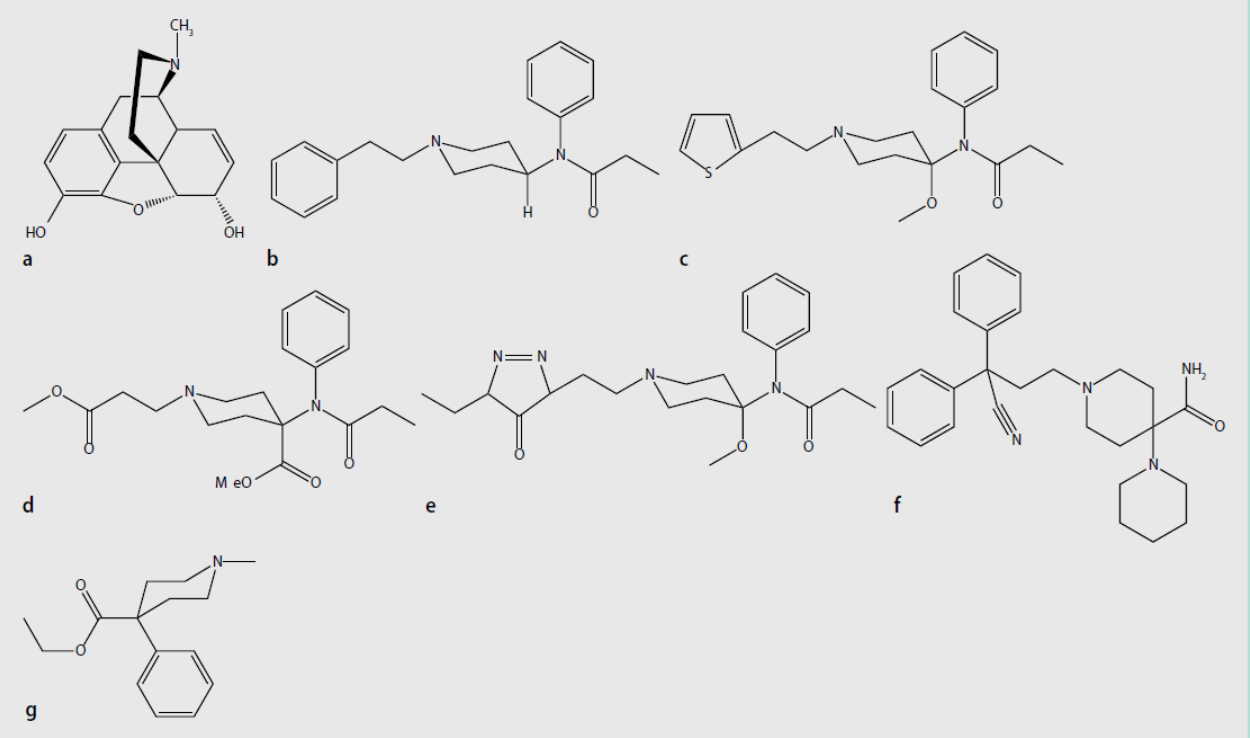


Figure 4: Chemical structural formulas of clinically used opioids[47].

a. Morphine b. Fentanyl c. Sufentanil d. Remifentanil e. Alfentanil f. Piritramid g. Pethidine

4.3.1 Remifentanil:

Remifentanil is unique ultra-short-acting selective μ-opioid receptor agonist. It is characterized by very short context-sensitivity half-life (3-4 minutes) (figure 5), as it is metabolized by unspecific blood and tissue esterases and eliminated independently of liver or renal function, and hence has predictable pharmacokinetics[48]. At the beginning of remifentanil use, relatively large doses were administered (1-5μg/kg/min) with stable intraoperative hemodynamics and early extubation and awakening at the end of the procedure. Because of some associated complications such as muscle rigidity and bradycardia, smaller doses (0.3 and 0.4 μg/kg/min) were

examined in context of cardiac surgery and found to be effective and safe [49]. Patients treated with remifentanil may suffer from severe pain immediately postoperatively[50].

Generally, in comparison with other short acting opioids in general anaesthesia (GA), remifentanil was associated with clinical signs of deeper analgesia and anaesthesia, more bradycardia, more hypotension, less hypertension, faster recovery, more frequent postoperative analgesic requirements, fewer respiratory events requiring naloxone and more postoperative shivering with no overall impact on postoperative nausea[50].

A meta-analysis was done for studies using remifentanil in patients undergoing cardiac surgery. It has been suggested that remifentanil may reduce cardiac biomarker release, ventilation time and hospital LOS[51]. At the beginning of FTCA era, Myles and Colleagues [52] discussed the choice of anaesthetic agents, and they reached a logical conclusion favoring low-dose opioid anaesthetic use.

4.3.2 Sufentanil:

Sufentanil was first synthetized in 1973. It took about 10 years to be considered as potent opioid and can stand in front of routine use of fentanyl at early eighties. The potency of intravenous sufentanil is 5-10 times higher than fentanyl. The suggested dose of sufentanil in balanced anaesthesia during medium- long surgery is 0.5-1.5µg/kg with supplemental dose of 0.15-0.7µg/kg and the total procedure dose 2-3µg/kg[53].

The continuous infusion doses range from 0.3-1µg/kg/h. The safety of this management is determined by its context-sensitive half-time. In comparison with remifentanil, sufentanil has longer context sensitive half time (30-35min) after 4-hours supply. After that, sufentanil curve increases non-linearly[53](Figure 5). This may have impact on time of eligibility to be transferred in lower-dependency unit, and hence the overall costs.

The pharmacokinetics of sufentanil follows the three compartmental model. Before CPB, the linearity of the pharmacokinetics can accurately predict sufentanil concentrations[54]. During extracorporeal circulation, marked fluctuation in plasma level was observed due to redistribution from the lungs and muscles following a primary decrease in the drug concentration, mostly resulting from hemodilution and redistribution to the cardiopulmonary depot. This substantially prolongs the half time of elimination.

In Vitro, it has found that both remifentanil and sufentanil has cardio-protective effect against re-oxygenation hypoxia[55]. Moreover, sufentanil preserves hemodynamic parameters as well as echocardiographic indices of LV function in patients with ischemic heart disease [56]. This stable hemodynamic effects are similar between the patients receiving remifentanil and sufentanil, with shorter time to recovery of spontaneous breathing and tracheal extubation in remifentanil patients[57]. Contrary to remifentanil, the intraoperative use of sufentanil does not require high postoperative analgesia.

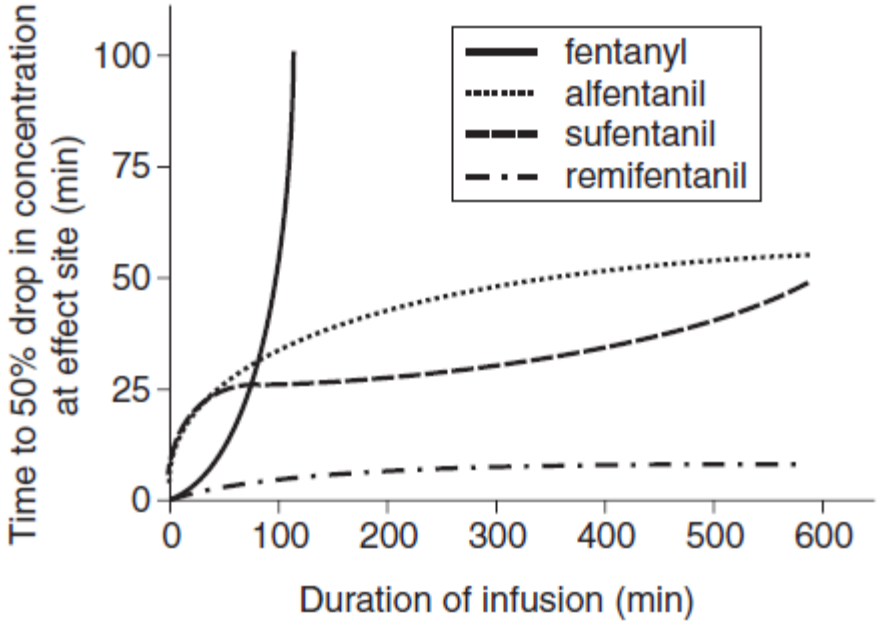


Figure 5: Context-sensitive half-times of remifentanil and the other 4-anilidopiperidine opioids[48].

5. Objective of the work

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 ventilation time (i.e. time from arrival on the post-anaesthesia care unit until tracheal extubation), length of stay in the post-anaesthesia care unit, visual analogue pain scores and piritramide consumption on the day of the operation. The 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.

6. Methods

This retrospective observational study was performed in a single university-affiliated heart centre, was approved by the local research ethics committee and individual patient consent was waived. In the period from February to July 2017, we were obliged to change our 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 post-anaesthesia care unit during this time period. This group was compared to an historical group of patients from the same time period the previous year (February to July 2016) who had received a continuous remifentanil infusion according to our standard fast-track protocol [2].

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 cardiopulmonary 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 $\mu g.kg^{-1}.h^{-2}$ until sternotomy, 0.5 $\mu g.kg^{-1}.h^{-2}$ until cardiopulmonary

bypass and 0.25 μg.kg^{-1}.h^{-2} after weaning from cardiopulmonary 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 post-anaesthesia care unit. For postoperative analgesia, metamizole 1g was given before extubation. 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. 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 operation room to post-anaesthesia care unit, anaesthesia was maintained with remifentanil 0.1-0.15 μg.kg^{-1}.min^{-2} and propofol 2mg.kg^{-1}.h^{-2}. Postoperative analgesia was commenced immediately after arrival in the post-anaesthesia care unit as a bolus of piritramide 0.1 mg.kg^{-1} and intravenous metamizole 1g. 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 operation all patients had to fulfill the fast-track criteria. Patients were admitted to the post-anaesthesia care unit if they were in a stable haemodynamic condition with a core temperature of at least 36°C. Both the surgeon and the anesthetist agreed to a fast-track pathway for each patient. The post-anaesthesia care unit operated daily, Monday to Friday from 10:00 h to 22:30 h. It was managed by anaesthetists and nursing staff with a nurse to patient ratio of 1:3 and physician to patient ratio of 1:4.

Patients' tracheas were extubated when they fulfilled the extubation criteria (table 2). Patient controlled analgesia (PCA) was offered to patients with a high visual analogue pain score and high analgesic consumption, either in post-anaesthesia care unit or later in the intermediate care unit, according to the attending physician. All patients were 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 2).

All patients received 4 mg dexamethasone before induction of anaesthesia as postoperative nausea and vomiting prophylaxis. Upon arrival at post-anaesthesia care unit, all female patients, patients scheduled for thoracotomy or patients with a post-operative nausea and vomiting history received 1.25 mg droperidol. Ondansetron 4mg was added in patients with a history of postoperative nausea and vomiting. Postoperative delirium was scored before transfer using the

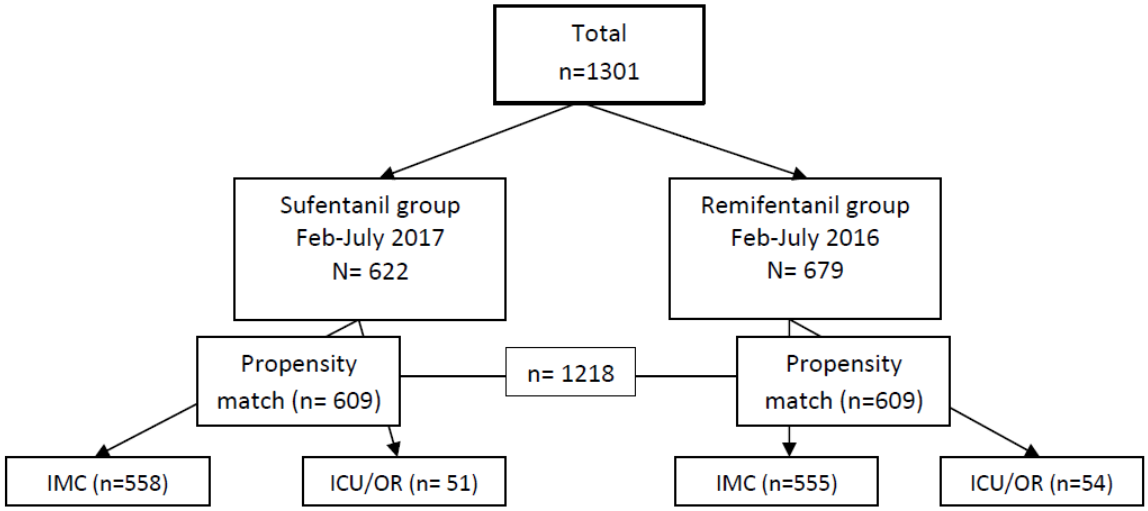
nursing delirium screening scale (Nu-DESC), where ≥2 is considered positive. Patients transferred from the post-anaesthesia care unit to the intensive care unit (or directly back to the operating room), were considered fast-track failure patients.

For data collection, our clinical information system iMedOne® (Deutsche Telekom Healthcare and Security Solutions GmbH, Germany) and our machine-readable patient's chart Medlinq® (Medlinq Softwaresysteme GmbH, Hamburg, Germany) were used. 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 length of surgery, and cardiopulmonary bypass and aortic cross clamp times. Pairs were matched 1:1 with their nearest neighbor 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 Fishers 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.

7. 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 of 609 patients (Figure 6).

Figure 6: Study flowchart for patients included in the study.



PACU, post-anaesthesia care unit; FT, fast-track; IMC, intermediate care unit; ICU, intensive care unit; OR, operating room

The baseline characteristics and operative data for patients included in the study are shown in table 3.

Ventilation time (i.e. time from arrival on post-anaesthesia care unit until tracheal extubation) and post-anaesthesia care unit-length of stay were significantly longer in the sufentanil group compared with the remifentanil group (Figures 7 and 8). 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 4).

Table 3: Baseline characteristics and operative data for patients included in the study. Values are mean (SD) or number (proportion).

	FT-Sufentanil group n=609	**FT-Remifentanil group n=609**	**p value**
Age; years	65 (10)	65 (12)	
Sex; female	170 (27.9%)	145 (23.8%)	
Logistic Euroscore	5.05 (6.0)	5.63 (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 creatinine level; µmol $.l^{-1}$	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
• 1x Valve replacement/repair	188 (30.8%)	193 (31.6%)	0.804
• 2x Valve replacement/repair	14 (2.2%)	13 (2.1%)	0.999
• 3x Valve replacement/repair	1 (0.16%)	2 (0.32%)	0.999
• CABG+1x Valve replacement/repair	58 (9.5%)	60 (9.8%)	0.922
• CABG+2xValve replacement/repair	1 (0.16%)	2 (0.32%)	0.999
• CABG+ Others	5 (0.82%)	6 (0.98%)	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 7. A comparison of the ventilation times between the sufentanil group and the remifentanil group. IQR, Interquartile range; UQ, upper quartile; LQ, lower quartile.

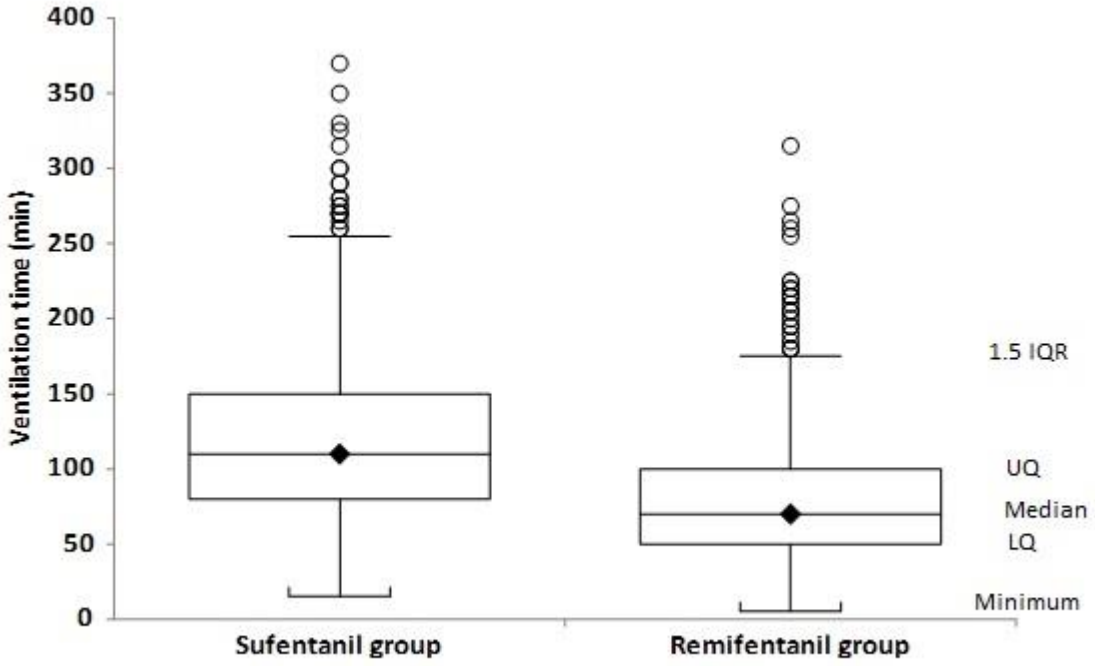
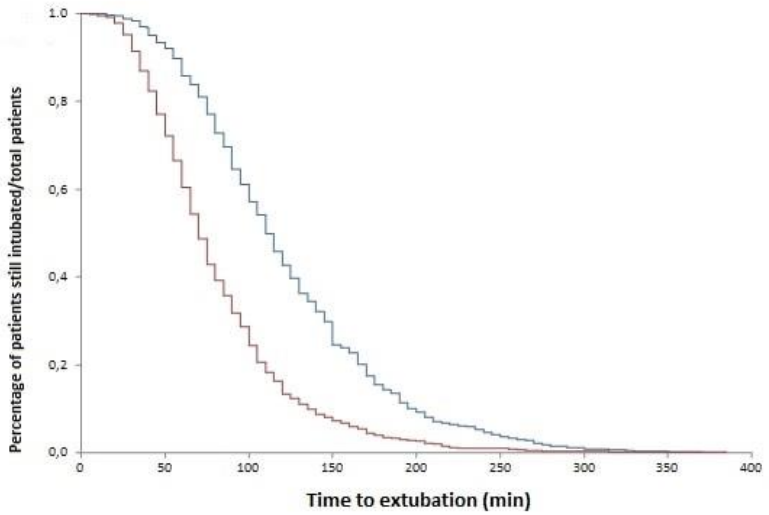


Figure 8. A comparison of the time to tracheal extubation between the sufentanil group (blue) and the remifentanil group (red).



Piritramide requirement during post-anaesthesia care unit stay was significantly higher for patients in the remifentanil group compared with those in the sufentanil group. There was no difference in patient controlled analgesia requirement between the groups either during their stay in the post-anaesthesia care unit or afterwards during their remaining hospital stay. The mean (SD) visual analogue pain score at the end of post-anaesthesia care unit stay was significantly lower in the sufentanil group compared with the remifentanil group (table 4).

Table 4: Postoperative outcome parameters for patients included in the study. Values are median (IQR [range]), mean (SD) or number (proportion).

	FT-Sufentanil group	**FT-Remifentanil group**	**p value**	**95% Confidence Interval of the Difference**
Ventilation time; min	110 (80-150 [15-370])	70(50-100 [5-315])	**<0.001**	36.3 to 48.3
PACU-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	-11.9 to 4.37
Hospital length of stay; d	14.1 (6.1)	15.5 (8.8)	**0.020**	-2.22 to -0.50
Visual analogue pain score (VAS)	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-PACU PCA requirement	11 (1.8%)	17 (2.7%)	0.339	N/A
Out-PACU PCA requirement	62 (10.1%)	55 (9.0%)	0.559	N/A

PACU, post-anaesthesia care unit; IMC, intermediate care unit; LOS, length of stay; PCA, patient controlled analgesia

Mean sufentanil consumption was 0.969 $\mu g.kg^{-1}.h^{-2}$, with a mean (SD) total consumption of 3.100 (0.100) $\mu g.kg^{-1}$. 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 5).

Table 5: Postoperative complications for patients included in the study. Values are number (proportion).

	FT-Sufentanil group	FT-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≥2)	9 (1.8%)*	8 (2.4%)§	0.721
Deaths	1 (0.16%)	4 (0.6%)	0.374

*n=483 §n=321

Nu-DESC, nursing delirium screening scale

8. Discussion

We have demonstrated that a remifentanil infusion in cardiac surgery patients managed in a specialised post-anaesthesia care unit using a fast-track protocol resulted in a significantly shorter ventilation time and length of stay in the post-anaesthesia care unit compared with patients who received a sufentanil infusion. However, the remifentanil group consumed more analgesics 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 [58], we demonstrated a reduction in ventilation time and post-anaesthesia care unit 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 can be noticed (figure 8). The explanation for shorter ventilation times in our study might be differences

in our fast-track protocol. Bhavsar et al. attempted to wean patients one hour after their arrival in the cardiac recovery unit whereas our weaning protocol started immediately after fulfillment of predefined weaning criteria. Another explanation might be the different opening hours of the post-anaesthesia care units; in Bhavsar et al.'s study the opening hours were from Monday morning to Saturday afternoon whereas our post-anaesthesia care unit was closed overnight. Grass et al. [20] 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 consumed 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 [59]. 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 [60, 61].

The increased requirement for piritramide in the remifentanil group is in agreement with previous studies [50, 58, 60]. 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. [60] demonstrated similar differences in pain scores during the first hours of weaning, although Gerlach et al. [61] did not find any differences in repeated pain score measurements within the first 12 hours postoperatively. In our study the need for patient controlled analgesia due to high analgesic requirement caused by severe pain was comparable between the two groups, both during and after post-anaesthesia care unit stay.

The sufentanil patients stayed longer in the post-anaesthesia care unit before intermediate care unit transfer. Although this was statistically significant it is probably not clinically relevant; transfer of patients between different units is subjected 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 [58, 60]. This can be explained by different fast-track

pathways between studies (intensive care unit vs. post-anaesthesia care unit) 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. The use of remifentanil and the resultant postoperative pain might also possibly be the cause of this difference in hospital length of stay and could not be excluded. However, 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 post-anaesthesia care unit directly to the intensive care unit or a return to the operating theatre. There was a comparable low fast-track failure rate of 8% in both groups. This is in agreement with Lison et al. [60] who excluded approximately 10% in each of their groups due to failure in completion of the fast-track pathway. In contrast to Lison et al. [60], we did not find a high incidence of postoperative nausea and vomiting in our remifentanil group. This may be due to our post-operative nausea and vomiting prophylaxis strategy and a remifentanil systematic review supports our results [50]. We did not find any differences between our groups in the incidence of postoperative delirium, assessed before transfer from the post-anaesthesia care unit, suggesting that the type of opioid per se is not a risk factor for 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 [62]. A ventilation time of more than 300 minutes, 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 [63].

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’ i.e. 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 post-anaesthesia care unit 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.

9. Publication manuscript

Anaesthesia 2019, 74, 602–608 doi:10.1111/anae.14572

Original Article

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

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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.

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Accepted: 8 December 2018
Keywords: fast-track cardiac anaesthesia; postoperative ventilation; recovery area; remifentanil; sufentanil
*Presented in part at the Annual Meeting of the European Association of Cardiothoracic Anaesthetists (EACTA), Manchester, UK, September 2018.

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 espeically 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 $\mu g.kg^{-1}.h^{-2}$ until sternotomy; 0.5 $\mu g.kg^{-1}.h^{-2}$ until, and during, bypass; and 0.25 $\mu g.kg^{-1}.h^{-2}$ 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 $\mu g.kg^{-1}.min^{-2}$ 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 $\mu g.kg^{-1}.min^{-2}$ 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 cmH_2O, PEEP 0–5 cmH_2O, $F_iO_2 \leq 40\%$
- Arterial blood gases; $PaO_2 \geq 13.3$ kPa, $PaCO_2 \leq 5.8$ kPa
- $SvO_2 \geq 70\%$, 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; $PaO_2 \geq 13.3$ kPa, $PaCO_2 \leq 5.8$ kPa with F_iO_2 0.4
- Normal SvO_2
- Acceptable tidal volumes with pressure support of 8 cmH_2O and PEEP of 5 cmH_2O
- 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; $PaO_2 > 12$ kPa, $PaCO_2 < 6.1$ kPa, $S_pO_2 > 96\%$ 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 SvO_2
- Cardiac enzymes and CXR warranting no further intervention
- Visual analogue pain score < 4

SvO_2, 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 (piritramide) 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 $\mu g.kg^{-1}.h^{-2}$, with a mean (SD) total consumption of 3.100 (0.100) $\mu g.kg^{-1}$. 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).

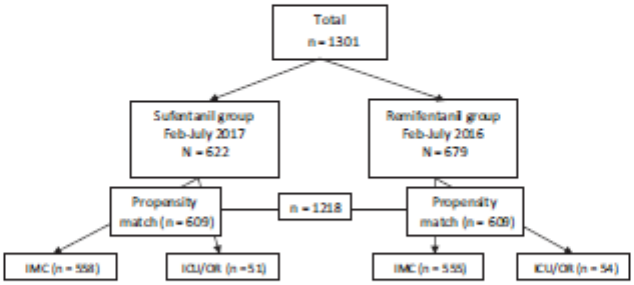

Figure 1 Study flowchart for patients included in the study. IMC, intermediate care unit; ICU, intensive care unit; OR, operating room

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; $\mu mol.l^{-1}$	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+2 × 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.

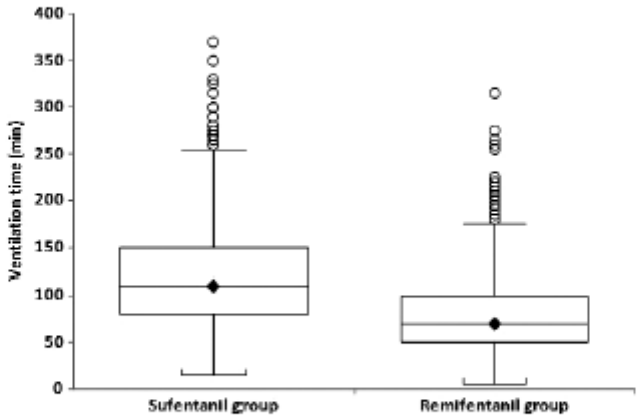

Figure 2 A comparison of ventilation times between the sufentanil group and the remifentanil group. Horizontal line is median, boxes are IQR, lower whiskers are lowest range and upper whiskers are 1.5 upper IQR.

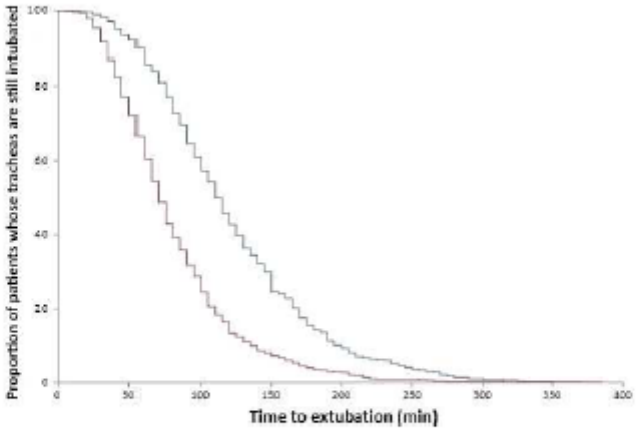

Figure 3 A comparison of the time to tracheal extubation between the sufentanil group (blue) and the remifentanil group (red).

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 ≥ 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.
[a] n = 483 [b] n = 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.

Acknowledgements

No external funding or competing interests declared.

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10. Summary

Dissertation to obtain the academic degree Dr. med

A comparison of sufentanil versus remifentanil in fast-track cardiac surgery patients Submitted by:

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Submitted in February 2019

The main drives of development of fast track cardiac anaesthesia are the increase burden of health care cost and the shortage of intensive care beds. Fast track (FT) is multidisciplinary process that leads to rapid patient recovery and discharge without affecting morbidity and mortality. Fast track cardiac anaesthesia (FTCA) was proved to be safe, efficient and economically effective.

Leipzig FT protocol was first introduced in November 2005 for elective cardiac surgery patients in the heart center of Leipzig University. It is characterized by using intraoperative remifentanil as main opioid with treating the patients postoperatively in post-anaesthesia care unit (PACU) completely bypassing ICU admission.

Remifentanil was unavailable in Germany from February to July 2017, therefore the protocol had to be modified and sufentanil was used instead. The aim of this retrospective study was to compare the effects of remifentanil and sufentanil on the well-established FT concept. The primary end points were ventilation time, LOS in PACU (LOS PACU), the visual analogue score (VAS) and the piritramide consumption on the day of operation. The secondary end points were LOS in intermediate care (LOS IMC), hospital LOS, FT failure (FTF), in-hospital mortality and postoperative complications such as postoperative nausea and vomiting (PONV), delirium and the incidence of reintubation.

All cardiac surgery patients consecutively admitted to PACU during the period from February to July 2017 (n=622), received sufentanil (FT-S), were compared to patients (n=679) from the same time period of the previous year treated with continuous remifentanil infusion (FT-R) according to the standard FT protocol. To minimise selection bias and to obtain comparable groups, we used a 1:1 nearest neighbour propensity score matching approach resulted in total 1218 patients divided in 2 equal groups.

In FT-R, an uninterrupted continuous infusion of remifentanil (0.2-0.3 µg/kg/min) was used for maintenance of anaesthesia throughout the whole operation. In FT-S, a continuous infusion of sufentanil was used during maintenance of anaesthesia as follows: 1 µg/kg/h until sternotomy, 0.5 µg/kg/h until cardiopulmonary bypass and 0.25 µg/kg/h until chest closure, then the infusion was stopped. Otherwise, the Leipzig FT protocol was used as previously published.

Remifentanil was more effective in reducing time to extubation (by 40 minutes) and length of stay in the post anaesthetic care unit during fast track cardiac anaesthesia than sufentanil. There was an increased need of piritramide when remifentanil was used. The hospital length of stay was longer in remifentanil group. There were no differences between both groups regarding postoperative complications. Clinically, a detailed and time-directed weaning protocol is more important than the use of a specific opioid during fast track treatment in cardiac surgery patients.

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12. Appendix (Anlagen):

12.1 Declaration of Independence (Selbstständigkeitserklärung)

Erklärung über Die Eigenständige Abfassung Der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungs-behörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

Unterschrift

Datum 20.12.2018

12.2 Erklärung zu den beiträgen der Mitautoren bei diesem Publikationsmanuskript

Erklärung zu den Beiträgen der Mitautoren bei diesem Publikationsmanuskript.

Zakhary, W.Z.A. – Korrespondierender Autor des Publikationsmanuskripts: Erhebung, Zusammenführung, und Auswertung der präoperativen, intraoperativen und postoperativen Daten. Durchführung der statistischen Berechnungen und Literaturrecherche.

Turton, E.W.: Unterstützung der Formulierung und Hilfe bei der Veröffentlichung des Manuskripts.

Flo Forner, Anna: Unterstützung bei der statistischen Berechnungen.

von Aspern, K.: Durchführung der „Propensity score matching".

Borger, M.A.: Unterstützung bei der Formulierung.

Ender, J.K.: Maßgebliche Hilfe bei der Veröffentlichung und Betreuung des Manuskripts.

12.3 Publications

- Waseem Zakaria Aziz Zakhary, Edwin Wilberforce Turton, Joerg Karl Ender: *Post-operative patient care and hospital implications of fast track*. European Heart Journal Supplements 01/2017; 19(suppl A):A18-A22., DOI:10.1093/eurheartj/suw055

- Waseem Zakaria Aziz Zakhary, Edwin Wilberforce Turton, Joerg Karl Ender: *Do we really need more intensive care unit beds?*. 09/2016; 4(18)., DOI:10.21037/atm.2016.08.07

- Waseem Zakhary, Jacob Lindner, Sophia Sgouropoulou, Sarah Eibel, Stefan Probst, Markus Scholz, Joerg Ender: *Independent Risk Factors for Fast-Track Failure Using a Predefined Fast-Track Protocol in Preselected Cardiac Surgery Patients J Cardiothorac Vasc Anesth 29:1461-1465, 2015*. Journal of cardiothoracic and vascular anaesthesia 08/2016; 31(3)., DOI:10.1053/j.jvca.2016.01.030

- Aniruddha Ramesh Janai, Wilfried Bellinghausen, Edwin Turton, Carmine Bevilacqua, Waseem Zakhary, Martin Kostelka, Farhad Bakhtiary, Joerg Hambsch, Ingo Daehnert, Florian Loeffelbein, Joerg Ender: *Retrospective Study of Complete Atrioventricular Canal Defects: Anaesthetic and Perioperative Challenges*. Annals of Cardiac Anaesthesia 01/2018; 21(1):15-21., DOI:10.4103/aca.ACA_110_17

- Grass C, Federica Stretti, Zakhary W, Turton E, Sgouoropoulou S, Mende M, Ender J: *Impact of the post-anaesthetic care unit opening hours on fast-track success in cardiac surgery*. Minerva anestesiologica 02/2017; 83(2):155., DOI:10.23736/S0375-9393.16.11308-2

12.4 Acknowledgement:

Firstly, I would like to express my sincere gratitude to my advisor **Prof. Dr. med. habil. Jörg Ender** for the continuous support of my study and related research, for his patience, motivation, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. My heartfelt appreciation goes to **Univ Prof. Dr. med. Sebastian Stehr** whose comments and suggestions were of inestimable value for my study.

I would especially like to thank my family. My wife, **Nahrin** and my sons, **Justus** and **Antonius** have been extremely supportive of me throughout this entire process and has made countless sacrifices to help me get to this point.

I would like to thank my friends and colleagues **Aniruddha Ramesh Janai** and **Edwin Turton** for their frequent help and support.