Comparative efficacy and safety of remifentanil and fentanyl in 'fast track' coronary artery bypass graft surgery: a randomized, double-blind study

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This multi-centre, parallel group, randomized, double-blind study compared the efficacy and safety of high-dose remifentanil administered by continuous infusion with an intermittent bolus fentanyl regimen, when given in combination with propofol for general anaesthesia in 321 patients undergoing elective coronary artery bypass graft surgery. A significantly lower proportion of the patients who received remifentanil had responses to maximal sternal spread (the primary efficacy endpoint) compared with those who received fentanyl (11% *vs* 52%; $P<0.001$). More patients who received remifentanil responded to tracheal intubation compared with those who received fentanyl (24% *vs* 9%; $P<0.001$). However, fewer patients who received remifentanil responded to sternal skin incision (11% *vs* 36%; $P<0.001$) and sternotomy (14% *vs* 60%; $P<0.001$). Median time to extubation was longer in the subjects who received remifentanil than for those who received fentanyl (5.1 *vs* 4.2 h; $P=0.006$). There were no statistically significant differences between the two groups in the times for transfer from intensive care unit or hospital discharge but time to extubation was significantly longer in the remifentanil group. Overall, the incidence of adverse events was similar but greater in the remifentanil group with respect to shivering ($P<0.049$) and hypertension ($P<0.001$). Significantly more drug-related adverse events were reported in the remifentanil group ($P=0.016$) There were no drug-related adverse cardiac outcomes and no deaths from cardiac causes before hospital discharge in either treatment group.

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Cardiovascular stability is an essential prerequisite for cardiac anaesthesia, where myocardial protection is vital in patients who already have compromised cardiovascular function. Traditionally, profound intraoperative analgesia has been provided by using high doses of opioids to suppress hormonal and metabolic stress responses to surgical stimuli. This regimen resulted in improved morbidity and mortality after cardiac surgery. [1 2] However, high doses or prolonged administration of conventional opioids can result in their accumulation, leading to postoperative respiratory depression and prolonged stay in the intensive care unit (ICU).[2] In many centres, economic considerations have resulted in the adoption of cardiac anaesthesia regimens using low- to medium-dose opioids administered intermittently aiming to reduce time to extubation and postoperative ICU and hospital stay. Such regimens have been shown to allow reductions in extubation times and in hospital stay[3–5] and recent studies have indicated that there is no adverse influence on the incidence of postoperative sequelae in low-risk cardiac patients.[6 7] However, there is

evidence that the level of intraoperative analgesia (hypertension and tachycardia) may influence the risk of postoperative myocardial infarction in all patients undergoing cardiac surgery. [2 8]

Remifentanil hydrochloride is a potent μ-opioid receptor agonist characterized by a predictable rapid offset of action as a result of its metabolism by non-specific esterases in blood and other tissues. The aim of this study was to compare the efficacy and safety of remifentanil using a total i.v. anaesthesia technique in combination with propofol (high-dose opioid regimen) with a commonly used low/medium-dose fentanyl plus propofol regimen in patients undergoing elective coronary artery bypass graft (CABG) surgery who were potentially eligible for early extubation/ICU discharge.

Patients and methods

This prospective, randomized, double-blind, parallel group study was conducted at 23 centres in 10 countries. Local Ethics Committee or Review Board approval was obtained at each study centre and informed written consent was obtained from each patient. Patients aged ⩾18 yr with ASA status II–IV and ejection fraction >0.3, undergoing elective CABG surgery were randomized to receive either remifentanil or fentanyl as part of a total i.v. anaesthesia technique with propofol. A total of 321 patients were recruited, of whom 24 were treated on an open label basis as 'pilot' patients and 297 were randomized to treatment.

All patients included in the study were potentially eligible for early extubation/ICU discharge. Patients with severely impaired left ventricular function (ejection fraction <0.3), significant arrhythmias, evidence of severe congestive heart failure, intra-aortic balloon assist device preoperatively, or severely impaired major organ function were excluded. Patients were also excluded from the study if they required preoperative inotropic support, or were undergoing CABG with simultaneous valve repair/replacement, or any other combined surgical procedure. Other exclusion criteria were body weight over 50% above ideal body weight, hypersensitivity to opioids or propofol and administration of opioids or long acting benzodiazepines within 12 h before the start of the study.

All patients were pre-medicated with diazepam 10 mg orally 1 h before surgery. Upon arrival to the anaesthetic area, midazolam 0.05 mg kg^{-1} i.v. was administered for sedation before placement of cannulae. Baseline systolic blood pressure (SBP) was recorded before instrumentation and a baseline blood sample was collected for cardiac enzyme analysis. Before induction of anaesthesia, each patient was given 100% oxygen for at least 3 min. Anaesthesia was induced with propofol 0.5 mg kg^{-1} followed by additional boluses of 10 mg every 10 s until loss of consciousness (LOC), which was defined as loss of response to verbal commands. At LOC, pancuronium 0.10–0.15 mg kg^{-1} was administered to facilitate tracheal intubation and propofol maintenance infusion 3 mg kg^{-1} h^{-1} was started. Simultaneously, as indicated by randomization, the loading dose and infusion of remifentanil placebo loading dose, 1 μg kg^{-1} min^{-1} infusion or fentanyl (15 μg kg^{-1} loading dose, placebo infusion) were started. Tracheal intubation was performed at least 6 min after the start of opioid administration.

Management of inadequate and excessive anaesthesia

During maintenance of anaesthesia, responses to surgical stimuli indicating inadequate anaesthesia were defined as one or more of the following:

- SBP >15 mm Hg above preoperative baseline or >140 mm Hg for ⩾1 min; arterial pressure (AP) >80 mm Hg for ⩾1 min during bypass.
- Heart rate (HR) >90 beats min^{-1} for ⩾1 min (pre-bypass); non-paced HR >100 beats min^{-1} for ⩾1 min (post-bypass).
- Somatic responses: gross movement, swallowing, grimacing, eye opening.
- Autonomic responses: lachrymation, sweating.

Inadequate anaesthesia was treated in a sequential manner beginning with simultaneous bolus dose administration (remifentanil 1 μg kg^{-1}, fentanyl 2 μg kg^{-1}) and infusion increments equivalent to 0.5 or 1.0 μg kg^{-1} min^{-1} remifentanil (unless there were intervening decreases). A maximum of three to six maintenance rate increases were allowed up to a maximum infusion rate of remifentanil 4 μg kg^{-1} min^{-1} or placebo equivalent. All infusion rate increases were preceded by a bolus dose. If a response was not controlled within 5 min of adjusting the opioid infusion rate or if the maximum infusion rate was reached, the propofol infusion rate was increased as required. If the response was still not controlled, other agents (e.g. sodium nitroprusside, beta-blockers) could be given. Once the patient had achieved a stable, non-responding status, the propofol infusion rate was then titrated back down but the opioid maintenance infusion was left at the higher rate unless hypotension occurred.

Excessive anaesthesia was defined as one or more of the following:

- SBP <80 mm Hg for ⩾1 min; AP <40 mm Hg for ⩾1 min during bypass.
- HR <40 beats min^{-1} for ⩾1 min.

Hypotension was treated by administration of fluids if the patient was hypovolaemic. Otherwise these responses were treated by decreasing the opioid and/or propofol infusion rate. The opioid maintenance infusion rate was reduced by 50% of the current rate or in decrements equivalent to remifentanil 0.25–0.5 μg kg^{-1} min^{-1}. If blood pressure fell rapidly, the opioid maintenance infusion rate decrease could be accompanied by simultaneous administration of vasopressors. Further vasopressor treatment was to be used if these interventions were not successful. Bradycardia was

treated by decreasing the opioid and/or hypnotic infusion rate and/or the use of anticholinergic drugs as required.

In addition to the 'treatment' of inadequate anaesthesia, the study procedure allowed preventative measures at the discretion of individual investigators. Study opioid bolus and infusion rate increases were allowed in advance of surgical stimuli to prevent anticipated responses up to a maximum infusion rate equivalent to remifentanil 4 μg kg^{-1} min^{-1}.

After surgery, once the patient was settled in the ICU, the opioid and propofol infusions were reset (remifentanil 1 μg kg^{-1} min^{-1}, placebo in the fentanyl group, propofol 0.5 mg kg^{-1} h^{-1} in both groups). The infusions were continued until the patient met the criteria for the start of weaning for extubation, that is, normothermia, haemodynamic stability (no uncontrolled arrhythmias, stable vital signs), no excessive bleeding (institutionally defined) and adequate urine output ($\geq$0.5 ml^{-1} kg^{-1} h^{-1}). The propofol infusion rate could be adjusted accordingly if additional sedation was required. If additional analgesia was required a bolus dose of open label morphine could be administered at the minimum dose necessary to provide patient comfort according to standard local practice and this was recorded as rescue treatment.

Once the patient had met the criteria for the start of weaning from study opioid infusion, a double-blind analgesic bolus was administered (morphine 0.15 mg kg^{-1} in the remifentanil group, placebo in the fentanyl group). The down titration period started 30 min later (as long as the patient still met the criteria for weaning from study opioid). The propofol infusion was stopped and the study opioid infusion was down-titrated at 10 min intervals in 50% decrements three to four times in order to maximize smooth transition to alternative regimens, and then discontinued. Weaning of the patient from the ventilator was started during commencement of this down-titration. If additional analgesia was required during this period, an open label bolus dose of morphine (minimum dose 0.05 mg kg^{-1}) was administered and recorded as rescue treatment.

Patients were extubated if the following criteria were met: responsive to commands; Sp_{O_2} $\geq$95% at FI_{O_2} $\leq$0.5, pH >7.25, Pa_{CO_2} $\leq$7.33 kPa and ventilatory frequency adequate to maintain oxygenation. If the patient had not met the criteria for beginning the extubation sequence by 4.5 h after entry into the ICU, the analgesic opioid bolus was administered at this time and the down-titration of the study opioid was then started 30 min later. Patients were eligible for transfer from ICU if stable conditions continued.

Monitoring

Vital signs were recorded immediately before induction of anaesthesia (baseline values) and at regular intervals throughout surgery and in the ICU. These consisted of SBP, DBP, MAP, HR, CVP, and Sp_{O_2}. During the pre-bypass period, patients' vital signs were recorded 1 min before and every minute for 5 min after each major surgical stress event (MSE), then every 15 min from the MSE until the next MSE. MSEs were defined as intubation, sternal skin incision, sternotomy, maximal sternal spread (MSS), and sternal wire placement. Arterial pressure was recorded at the start of cardiopulmonary bypass and every 15 min until the patient went off bypass.

After entry into the ICU, patients' vital signs were recorded immediately and at 15 min intervals thereafter until extubation. In addition, vital signs, pain, and sedation scores were recorded every 10 min during the down-titration of study opioid. Pain was assessed using a four-point patient self-rated scale (0=no pain, 1=mild, 2=moderate, 3=severe), while sedation was assessed using a five-point scale (1=fully awake and orientated, 5=eyes closed and cannot be roused by mild physical stimulation). Vital signs and pain and sedation scores were also recorded at 15, 30, 45, 60, 90, and 120 min after discontinuation of study opioid infusion.

12-lead ECG recordings were obtained within 14 days before surgery and on postoperative day 1, and at the end of day 5 or on the morning of day 6 (or day of hospital discharge if prior to this). Blood samples were obtained at 8, 16, 24, and 48 h after aortic cross clamp release for analysis of plasma cardiac enzyme concentrations (CK-CKMB).

Outcome measures

The primary efficacy endpoint was response to MSS. Secondary efficacy endpoints included responses to intubation, sternal skin incision, sternotomy, and sternal wire placement. Efficacy was evaluated by the number of patients who showed signs of inadequate anaesthesia and by the number of treatments for responses indicative of inadequate or excessive anaesthesia. Overall use of study drug, propofol and other medications were noted. Patients were continually assessed for occurrence of adverse events (including negative cardiac outcomes) throughout the perioperative period and up to the end of postoperative day 5 (or up to hospital discharge if this occurred earlier). Negative cardiac outcomes were defined as ventricular failure (requirement for postoperative intra-aortic balloon pump or ventricular assist device), myocardial infarction (CK-MB >50 unit $litre^{-1}$ and presence of new Q-waves on 12-lead ECG) or death from cardiac causes (e.g. ventricular failure or congestive heart failure) before hospital discharge.

Statistical analysis

The primary endpoint assumed a response rate of 7% and 18% for patients receiving remifentanil and fentanyl, respectively. One hundred and thirty five patients per treatment would have a power of 80% to detect this difference at a two-sided 5% level of significance. To compensate for withdrawals and to obtain additional safety

data, up to 300 randomized patients were to be included in the study. The study was stopped when 297 patients had been recruited because of time restriction. Patients were randomized to receive either remifentanil or fentanyl by assignment of treatment randomization details contained in a hidden entry envelope, which had been computer-generated before the study set-up. The hidden entry envelopes were allocated sequentially to each subject eligible for study entry and the corresponding treatment allocation and drug preparation was performed by a named person, independent to the conduct of the study. In most instances this was the hospital pharmacist.

All tests of statistical significance were two-sided and carried out at the 5% level. Logistic regression analyses were used to analyse the proportions of patients with responses to MSS. Estimates of the odds ratios and 95% confidence intervals were calculated. The weighted mean pain and sedation scores during the ICU down titration were analysed using the Wilcoxon rank sum test. The treatment differences in overall use of alternate analgesics until extubation, were analysed using logistic regression analysis.

The incidences of the most commonly reported adverse events (defined as occurring in at least 5% of patients in any treatment group) were analysed using Fisher's exact test.

Table 1 Patient characteristics (safety population)

	Remifentanil (n=172)	Fentanyl (n=149)
Gender		
Male	147 (85%)	132 (89%)
Female	25 (15%)	17 (11%)
Ethnic origin		
Caucasian/white	169 (98%)	147 (99%)
Oriental	0	1 (<1%)
Asian (not oriental)	2 (1%)	0
Other	1 (<1%)	1 (<1%)
Age (yr)		
Mean (range)	62 (37–78)	63 (38–76)
SD	8.8	8.4
Height (cm)		
Mean (range)	172 (150–191)	172 (152–190)
SD	7.9	7.8
Weight (kg)		
Mean (range)	79 (50–115)	80 (54–117)
SD	11.9	11.4
ASA status		
II	38 (22%)	33 (22%)
III	124 (72%)	103 (69%)
IV	10 (6%)	13 (9%)

Results

Three hundred and twenty one patients entered the study, 24 were treated on an open label basis and were not included in the intent-to-treat population for efficacy analyses although they were included in the population for safety data. The intent-to-treat population consisted of 297 patients, of whom 148 patients received remifentanil and 149 received fentanyl.

The two groups were well matched with regard to gender, ethnic origin, age, height, weight, and ASA status distribution (Table 1). The mean ejection fraction was similar in the remifentanil (0.62) and fentanyl (0.63) groups. Most patients required three arteries to be grafted (41% in the remifentanil group and 45% in the fentanyl group). Two patients in each group had previous CABG surgery. The median durations of surgery, of bypass, and of aortic cross clamping were comparable between the two groups. The median (SD) time from the start of study drug to skin closure was 3.67 h (1.85, 6.3) in the remifentanil group and 3.58 h (1.97, 8.7) in the fentanyl group. The median (SD) durations of bypass and of aortic cross clamping were 1.31 (0.45, 2.4) and 0.75 h (0.22, 3.6), respectively, in the remifentanil group and 1.23 (0.17, 2.85) and 0.73 h (0.08, 2.33), respectively, in the fentanyl group.

Efficacy

The incidence of inadequate anaesthesia responses to MSS (the primary efficacy endpoint) was significantly lower in the remifentanil group (11%) compared with the patients in the fentanyl group (52%; P<0.001, odds ratio remifentanil:fentanyl= 0.09, 95% CI 0.05, 0.18). The mean remifentanil infusion rate at the time of MSS was 1.42 μg kg^{-1} min^{-1} and the mean propofol infusion rate in the remifentanil group was 3.14 mg kg^{-1} h^{-1}. In the fentanyl group, the cumulative fentanyl bolus dose administered at this point was 19.67 μg kg^{-1} and the mean propofol infusion rate was 3.94 mg kg^{-1} h^{-1} .

Hypertension was the most common type of response in those patients who had an inadequate anaesthesia response, occurring in seven patients (5%) in the remifentanil group and 75 patients (50%) in the fentanyl group. There was a mean increase in SBP (from the pre-MSS value to the maximum within 5 min of MSS) of 6 mm Hg in the remifentanil group compared with a mean increase of 15 mm Hg in the fentanyl group (P<0.001). A tachycardic response was recorded in 10 patients (7%) in the remifentanil group and eight patients (5%) in the fentanyl group.

Overall, the weighted mean infusion rate for remifentanil (R) during maintenance of anaesthesia (from pre-bypass to end of surgery) varied between 1.29 (0.69) μg kg^{-1} min^{-1} pre-bypass; 1.23 (0.73) μg kg^{-1} min^{-1} during bypass; 1.21 (0.77) μg kg^{-1} min^{-1} post-bypass. Fentanyl (F) cumulative bolus doses were 7.38 (3.63) μg kg^{-1} pre-bypass; 3.16 (1.56) μg kg^{-1} during bypass; and 2.92 (1.63) μg kg^{-1} post-bypass. Propofol varied between (R) 2.98 (0.69) *vs* (F) 3.58 (0.99) mg kg^{-1} h^{-1} pre-bypass; (R) 2.86 (0.45) *vs* (F) 3.46 (1.44) mg kg^{-1} h^{-1} bypass; (R) 2.8 (0.78) *vs* (F) 3.45 (1.4) mg kg^{-1} h^{-1} post-bypass; (R) 2.72 (0.85) *vs* (F) 3.32 (1.17) mg kg^{-1} h^{-1} end of surgery.

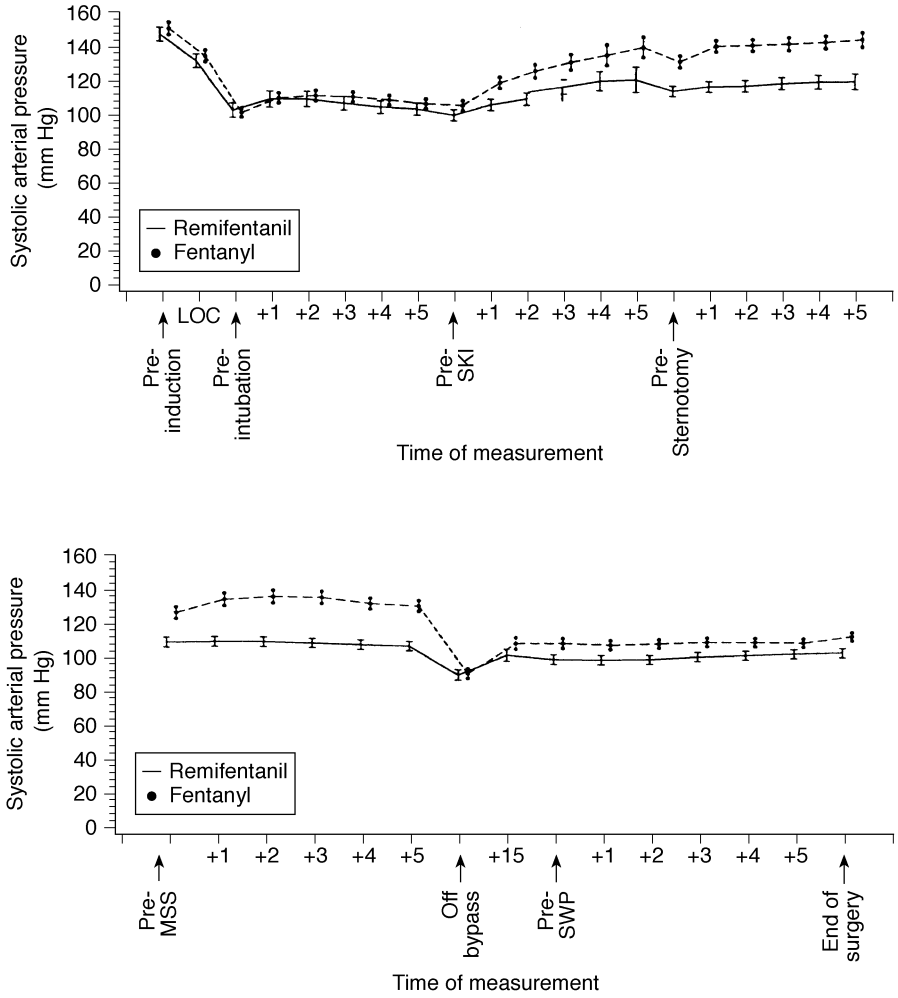

Fig 1 Mean (95% CI) intraoperative SBP in the remifentanil and fentanyl anaesthesia groups (intent-to-treat population).

During tracheal intubation, more patients in the remifentanil group showed signs of inadequate anaesthesia compared with those in the fentanyl group (R 24%, F 9%, $P<0.001$). Response to sternal skin incision (R 11%, F 36%, $P<0.001$), sternotomy (R 14%, F 60%, $P<0.001$) and MSS (R 11%, F 52%, $P<0.001$) were significantly and clinically less in the remifentanil group. During sternal wire placement no statistical or clinically significant difference was noted (R 10%, F 13%).

Figures 1 and 2 present the SBP and HR profiles during key stages during surgery for both treatment groups. SBP fell after pre-induction (baseline) but remained stable within each treatment group compared with baseline values. SBP values were higher in the fentanyl group pre- and post-skin incision compared with remifentanil values at similar time intervals. HR remained stable and similar between treatment groups compared with pre-induction values.

More patients in the fentanyl group (92%) received medication to treat inadequate anaesthesia responses compared with the patients who received remifentanil (53%). Conversely, more patients in the remifentanil group (82%) received medication to treat excessive anaesthesia responses compared with the patients who received fentanyl (60%).

Table 2 summarizes the postoperative recovery times in the remifentanil and fentanyl anaesthesia groups. The median times to eligibility for weaning for extubation, and for the actual start of the extubation sequence, were longer in the remifentanil group than in the fentanyl group ($P<0.05$). The median times to eligibility for, and the actual start of extubation were also significantly longer in the remifentanil group than in the fentanyl group ($P<0.05$). The median times to eligibility for, and for actual transfer from the ICU to less intense monitoring were similar in the remifentanil and fentanyl groups. The median times to hospital discharge were also similar in the remifentanil and fentanyl groups and a similar proportion of patients in each group (17% R, 20% F) were discharged by the end of postoperative day 5 or morning of day 6.

Pain and sedation scores were assessed at scheduled times during the ICU down titration period and following discontinuation of study drugs. The weighted mean pain score during the ICU down-titration/transition period was

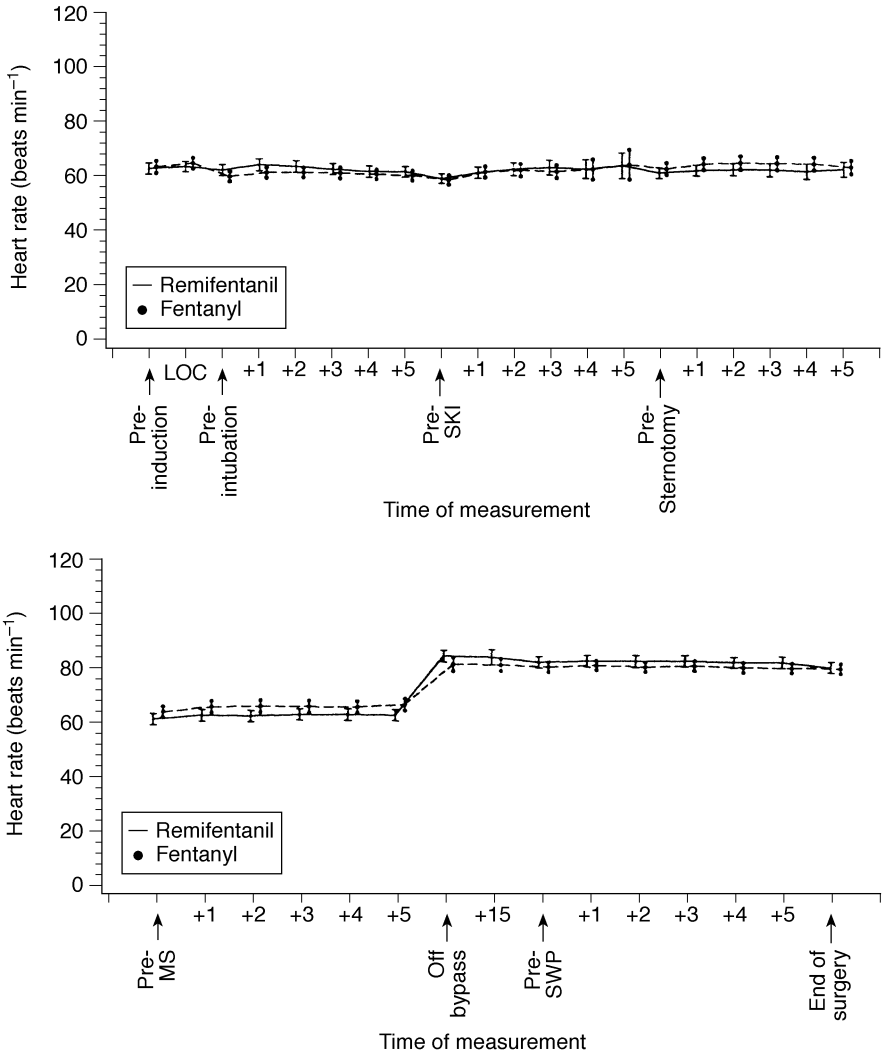

Fig 2 Mean (95% CI) intraoperative HR in the remifentanil and fentanyl anaesthesia groups (intent-to-treat population).

lower in the remifentanil group (0.21) compared with the fentanyl group (0.48). However, no significant difference in the change from baseline in pain scores between the two groups (P=0.174) was noted. A significantly higher proportion of patients in the remifentanil group required additional analgesia during the period from the end of surgery until extubation compared with the fentanyl group (81% *vs* 69%; P=0.02).

During the ICU transition period, the weighted mean sedation score was slightly but significantly higher in the remifentanil group (score 3.61) compared with the fentanyl group (score 2.92; P<0.001).

Safety and tolerability

Both anaesthetic regimens were well tolerated. In total, 138 patients (80%) in the remifentanil group and 113 patients (76%) in the fentanyl group experienced at least one adverse event (P=0.347). The most common adverse events recorded during the study (defined as events occurring in ⩾5% of patients in either treatment group) are listed in Table 3. Overall, the incidences of these events were similar in the remifentanil and fentanyl anaesthesia groups, except for hypertension and shivering which had a significantly higher incidence in the remifentanil group compared with the fentanyl group (P<0.001 and P=0.049, respectively). Both of these events were most commonly reported during the ICU period. Significantly more drug-related adverse events were reported in the remifentanil group compared with the fentanyl group (R 44% *vs* F 31%, P=0.016). The most common drug-related adverse events were nausea (20% of patients in each group), vomiting (R 6%, F 8%) and shivering (R 11%, F 5%). The only significant differences in drug-related events between groups were hypertension during the immediate postoperative period (R 5%, F 0%, P=0.008) and postoperative ache(s) (R 2%, F 0%; P=0.016).

A total of 13 patients (remifentanil five, fentanyl eight) were withdrawn from the study because of adverse events. Of the remifentanil-treated patients who were withdrawn,

Table 2 Postoperative recovery times in the remifentanil and fentanyl anaesthesia groups (intent-to-treat population) *LIM=less intense monitoring

	Remifentanil (*n*=148)	Fentanyl (*n*=149)	*P*-value
Time (h) to eligibility for starting extubation sequence			
Median	2.4	1.8	
Range	0.0–4.6 (*n*=143)	0.0–4.8 (*n*=149)	0.038
Time (h) to actual start of extubation sequence			
Median	2.4	1.8	
Range	0.0–17.4 (*n*=145)	0.0–7.0 (*n*=149)	0.048
Time (h) to eligibility for extubation			
Median	4.9	4.1	
Range	0.2–48.6 (*n*=145)	0.4–20.2 (*n*=148)	0.016
Time (h) to actual extubation			
Median	5.1	4.2	
Range	0.2–48.6 (*n*=145)	0.4–20.2 (*n*=148)	0.006
*Time (days) to eligibility for transfer to LIM**			
Median	0.8	0.7	
Range	0.0–6.6 (*n*=145)	0.1–3.9 (*n*=147)	n.s.
*Time (days) to actual transfer to LIM**			
Median	1.1	0.9	
Range	0.0–6.7 (*n*=145)	0.1–3.9 (*n*=148)	n.s.
Time (days) to hospital discharge			
Median	6.9	6.1	
Range	0.0–27 (*n*=139)	0.1–58 (*n*=140)	n.s.

Table 3 Adverse events occurring in ⩾5% of patients in all study phases in either treatment group (Safety Population). * Fisher's exact test

Adverse event	Remifentanil (*n*=172)	Fentanyl (*n*=149)	*P* value*
Nausea	63 (37%)	58 (39%)	n.s
Vomiting	22 (13%)	20 (13%)	n.s
Atrial fibrillation	16 (9%)	15 (10%)	n.s
Shivering	21 (12%)	8 (5%)	0.049
Fever	17 (10%)	9 (6%)	n.s.
Postoperative complication	12 (7%)	9 (6%)	n.s.
Hypertension	15 (9%)	1 (<1%)	<0.001
Ache(s)	10 (6%)	5 (3%)	n.s.
Haemorrhage	10 (6%)	5 (3%)	n.s.
Hypotension	11 (6%)	4 (3%)	n.s.

two were withdrawn during the ICU anaesthesia phase, that is, from end of surgery until first down titration of the opioid infusion. In these patients anaphylactic reaction and bleeding from the chest wall, respectively, were given as the reason for patient withdrawal. Neither of these events was assessed as related to study drug. In a further three patients the phase of the adverse event was not specified. The events leading to withdrawal in these three cases were postoperative haemorrhage, left ventricular failure, and case of bleeding leading to haemodynamic instability, respectively. In the latter case, the event was considered possibly related to study drug. Of the fentanyl-treated patients who were withdrawn, one patient was withdrawn during the ICU anaesthesia phase, six during the ICU transition phase, that is, from first down-titration of opioid infusion until the infusion was discontinued and for one patient the phase was not specified. In four patients, the reason for withdrawal included bleeding or postoperative haemorrhage and two patients were withdrawn because of reasons which included myocardial ischaemia; a further two patients were withdrawn because of complete heart block and delayed recovery as a result of cerebral death. None of the events leading to withdrawal were classified as possibly related to study drug.

Serious adverse events were reported in 25 patients (15%) in the remifentanil group and in 12 patients (8%) who received fentanyl. The majority of events in both the remifentanil group (12/25, 48%) and the fentanyl group (8/12, 67%) involved the cardiovascular system. There were no reports of drug-related serious adverse events in the fentanyl group. In six patients in the remifentanil group the serious adverse events were considered to be related possibly to the study drug. These included three cases of hypertension, two of which were also associated with shivering. All three cases were considered related to the withdrawal of remifentanil during the transition to alternate analgesic regimens. There were three serious cases of respiratory depression in the ICU in the remifentanil group, all of which resolved. In one of these cases the patient had a history of sleep apnoea.

A similar proportion of patients in each group showed signs of ischaemia during the perioperative period (13% of patients in the remifentanil group and 10% of those in the fentanyl group; P =0.44). Only one of these episodes in the fentanyl group was reported as a drug-related adverse event. There was also no significant difference between the two treatment groups in the incidence of negative cardiac outcomes (ventricular failure, myocardial infarction or death as a result of cardiac causes). Ventricular failure was reported in two of 146 patients (1%) in the remifentanil group; myocardial infarction was reported in four of 146 patients (3%) and three of 148 patients (2%) in the remifentanil and fentanyl groups, respectively (P=0.689). There were no deaths as a result of cardiac causes before hospital discharge. None of the three deaths reported during the study were considered to be related to the study drug.

Discussion

Our data demonstrate that the combination of remifentanil (starting dose of 1 μg kg^{-1} min^{-1}) and propofol (starting dose 3 mg kg^{-1} h^{-1}) was significantly more effective than the low/medium-dose fentanyl regimen used in obtunding responses to the majority of MSEs studied, including the primary endpoint, MSS. An exception to this was the higher incidence of responses to tracheal intubation in the

remifentanil group compared with fentanyl-treated patients. One could argue that the high bolus dose of fentanyl at the start of anaesthesia enabled optimal obtunding of the stress response since the peak effects of fentanyl occur between 3 and 6 min after administration.[9] However, stable intubation conditions with remifentanil could be expected after 6 min of a continuous infusion.[10] It is, therefore, difficult to explain why higher response rates to intubation were observed with remifentanil.

Intraoperative infusion rates indicate that 1 $\mu g\ kg^{-1}\ min^{-1}$ was an appropriate starting dose for remifentanil, which could be subsequently titrated up or down to the effect required in the individual patient. The minimum and maximum dose of remifentanil administered, reflect the wide inter-patient variability in the dose required to achieve adequate analgesia with an opioid in combination with the hypnotic component. Similar variations in initial remifentanil dose requirements for cardiac surgery are reported in the recent literature. [11–15]

Hypertension was the most commonly treated inadequate anaesthesia response in both groups, although the incidence was much higher in the fentanyl group. The majority of patients in both treatment groups (78% remifentanil *vs* 77% fentanyl) were receiving beta-blockers before the start of study treatment, which may help explain the very low incidence of tachycardia observed as a response to the major stress events.

It is recognized that opioids interact with such agents and blunt the sympathetic response to stress events and may exacerbate bradycardic and hypotensive episodes. Indeed recent reports of clinically significant bradycardia with use of remifentanil in cardiac patients [16 17] have cautioned its use in such patient groups although our experience did not indicate clinically significant treatment differences in bradycardia. Where hypotension did occur, the episodes were transient and managed by appropriate measures which included fluid loading, infusion rate adjustments of remifentanil and propofol and pharmacological intervention as required.

After transport to the ICU, both groups received the same starting infusion of propofol in combination with an opioid infusion (placebo in the fentanyl group). The mean pain score during the ICU transition period (i.e. down titration to alternate postoperative pain management regimens) was comparable between treatment groups. The pharmacokinetic profile of remifentanil may be expected to result in a rapid offset of action. Indeed there were some reports of hypertension and shivering observed during the transition from a remifentanil regimen to an alternative postoperative regimen, which may have been as a result of suboptimal management of the rapid offset of effects of remifentanil with respect to transition to alternative analgesics. The transition to an effective alternative analgesic regimen is a key consideration in the postoperative management of the patient when using a remifentanil regimen. Morphine administration as adopted in this study, may not be the best solution for fast track anaesthesia, although its cautious use during remifentanil based cardiac anaesthesia may have its place. Alternative and effective transition regimens have been suggested in the literature. [14 18]

Patients who received the low/medium-dose fentanyl regimen were eligible for extubation and were extubated earlier than the patients who received remifentanil. This may relate to the higher level of sedation in the remifentanil-treated patients during the postoperative period, which may have influenced the investigators' decision as to whether to actively intervene in extubating an otherwise calm and sedated patient. Similar consideration in actively managing early extubation regimens has been reported in the literature.[19] It would, therefore, appear that proactive intervention may be necessary with regard to extubation when using this dose of remifentanil in combination with propofol for weaning. In contrast, alternate transition regimens to that administered in this study have demonstrated comparable or superior recovery compared with a fast track fentanyl regimen.[13 15]

Despite the longer time to extubation in the remifentanil group compared with fentanyl-treated patients, there were no statistically significant differences between the two groups in the median times to eligibility for, or actual transfer from the ICU to less intense monitoring or to hospital discharge. The data probably reflect the fact that although the protocol-specified anaesthetic and post-operative treatment regimens ensured that patients could be extubated within a reasonable timeframe, subsequent management of patients would largely have depended upon whether or not hospital procedures were in place to 'fast track' patients to hospital discharge. It was not possible to standardize these in this large multi-centre international study. This is supported by the fact that in the majority of cases where patients were not discharged from hospital by the end of postoperative day 5, the reasons listed included institutional practice rather than any influence of the anaesthetic regimen used. Similar observations have been reported in other studies in which early extubation and recovery has not always resulted in faster ICU and/or hospital discharge times.[4 7 20] In this regard, it is also notable that many of the studies that have demonstrated significant reductions in ICU and/or hospital stay were conducted at single centres, [4 7 21 22] reducing the impact of variations in procedures for extubation, ICU, and hospital discharge. However, in this study, the use of the 'high dose' remifentanil opioid regimen resulted in a similar duration of ICU stay and postoperative hospitalization as the fentanyl regimen.

Both anaesthetic regimens were well tolerated and the recorded adverse event profiles are typical of potent μ-opioid receptor agonists and predictable in these patients following CABG surgery. There was little difference in the overall incidence of adverse events between the remifentanil and fentanyl treatment groups, although the incidences of drug-related adverse events and of serious adverse events

were higher in the remifentanil group than in the fentanyl group. Postoperative shivering and hypertension can increase oxygen consumption and precipitate episodes of myocardial ischaemia, which may adversely influence outcome, including risk of myocardial infarction.[2 23] However, the increased frequency of hypertensive events in the remifentanil group compared with the fentanyl group was not associated with any significant difference in the incidence of perioperative negative cardiac outcomes.

The serious cases of postoperative respiratory depression observed in the remifentanil group is an unexpected finding given the rapid offset of action of remifentanil. However, of the three reported cases, one included a patient with an underlying sleep apnoea disorder. Administration of the active blinded morphine bolus doses in the remifentanil group may have contributed to the higher incidence of respiratory depression observed compared with the placebo-treated fentanyl group.

In summary, our data show that high-dose remifentanil in combination with propofol is effective and well-tolerated when used to provide anaesthesia in CABG patients. Importantly, the data show that the remifentanil regimen provided superior control of some of the major stress events, but not to intubation. Intraoperative haemodynamic stability was associated with both treatment groups but use of a high-dose remifentanil regimen did not compromise patients' overall recovery times compared with the low/medium-dose 'fast track' fentanyl regimen. However, transition from a remifentanil-based regimen to alternate postoperative pain management regimens must be carefully and proactively managed to ensure rapid and smooth transition to alternate analgesic regimens.

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