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Remifentanil infusion in association with fentanyl–propofol anaesthesia in patients undergoing cardiac surgery: effects on morphine requirement and postoperative analgesia

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Background. We have prospectively assessed the effects of remifentanil on morphine requirement in the first hour after emerging from general anaesthesia after elective coronary artery bypass surgery and in the first 12 h postoperatively, and pain and agitation scores in the first hour after emerging from general anaesthesia.

Methods. Twenty patients undergoing off-pump coronary artery bypass surgery, receiving standardized propofol–fentanyl-based anaesthesia, randomly received infusions of either remifentanil 0.1 $\mu g\ kg^{-1}\ min^{-1}$ (Group R, n=10) or saline (Group S, n=10), each infused at 0.12 $ml\ kg^{-1}\ h^{-1}$. Propofol and trial drug infusion were continued into the postoperative period until the patients were ready to be woken up. Postoperative analgesia was provided with morphine infusion commenced immediately after operation, and was additionally nurse controlled on the basis of a visual analogue scale (VAS) score (0–10). Agitation score was recorded using a VAS of 0–3.

Results. In the first hour after discontinuing propofol and trial infusion, morphine requirements were significantly higher in the remifentanil group (8.15 (SD 3.59) mg) compared with the saline group (3.29 (2.36) mg) (P<0.01). There was no difference in the total morphine given during the period after stopping propofol or in the total requirement in the first 12 h postoperatively. There was no significant difference in either pain scores or agitation scores between the two groups.

Conclusion. Use of remifentanil is associated with increased opioid requirement in the first hour after it has been discontinued.

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Patients undergoing cardiac surgery require haemodynamic stability not only in the intraoperative period, but also throughout the perioperative period in order to minimize undesirable cardiac ischaemia. Induction of anaesthesia, tracheal intubation, skin incision and sternotomy cause undesirable sympathetic activity. Opioids reduce such responses,[1–4] but use of high dose opioids in cardiac surgery can lead to prolonged sedation and delay in tracheal extubation.[5]

Remifentanil is an ultra-short-acting esterase-metabolized opioid (terminal half-life of 3.8–8.3 min and context-sensitive half-time of 3–5 min). It is structurally related to fentanyl and alfentanil and has selective μ-opioid agonist activity. *In vitro* and *in vivo* studies demonstrate rapid and extensive metabolism of this compound by ester hydrolysis.[1 3 6 7] Use of remifentanil during anaesthesia provides intense analgesia and decreased sympathetic response to surgical stimulation. It has been used to provide sedation in intensive care units. Addition of remifentanil to the perioperative regime may be beneficial with greater cardiovascular stability intraoperatively and during sedation immediately postoperatively.[8]

Remifentanil is now used in cardiac surgery because of its effect on haemodynamic stability. It has been proposed as potentially suitable for 'fast-tracking' patients after off-pump coronary artery (OPCAB) surgery as its short intense action allows early extubation. However, there is concern about its 'antanalgesic' effect, leading to unfavourable emergence from anaesthesia, which is characterized by a suspected increased opioid requirement[9 10] and agitation.

The evidence for this effect is equivocal. Studies of volunteers and non-cardiac surgery patients have concluded that there is no tolerance to remifentanil.[11–13] However, it is notable that previous studies have focused on the period 12–24 h postoperatively and not on the first hour.

The purpose of this prospective randomized double-blind controlled study was to determine the effects of remifentanil on postoperative analgesia requirement in patients undergoing OPCAB surgery. The main aim of the study was to assess the analgesic requirement in the first hour after stopping remifentanil infusion as well as for the 12 h after the end of surgery.

Methods

After local ethics committee approval and informed written consent, 20 adult patients undergoing elective OPCAB were recruited for this prospective double-blind study. The sample size was chosen on the basis of power calculation from a pilot study of morphine requirement. It was calculated that a sample size of 10 in each group would have 88% power using a two-tailed Student's *t*-test with a significance level of 0.05 for detecting a difference in morphine consumption of at least 100% during the first hour.

Inclusion criteria were elective OPCAB and age 18–75 years. Patients were excluded preoperatively if they gave a history of severely impaired cardiac function, severe pulmonary disease, diabetes mellitus, renal failure, drug dependence or uncontrolled hypertension. Those requiring emergency surgery were also excluded. Postoperative exclusions included reoperation, excessive bleeding and prolonged ventilation (>12 h).

The patients continued their usual medications including all cardiac drugs. All patients received standardized premedication with temazepam 20–30 mg, metoclopramide 10 mg and sucralfate 2 g, given 90 min before operation. All patients were monitored according to standard guidelines. In addition, direct arterial and central venous pressure monitoring was established. Anaesthesia was induced using target-controlled infusion (TCI) of propofol with the target at 2.5–4 $\mu g\ ml^{-1}$ (Astra–Zeneca, Macclesfield, UK), fentanyl 15 $\mu g\ kg^{-1}$ and rocuronium 1.5 $mg\ kg^{-1}$. The trachea was intubated 3 min after induction. The patients were ventilated with oxygen-enriched air (50% oxygen). Anaesthesia was maintained with TCI propofol with the target between 1.8 and 4 $\mu g\ ml^{-1}$, guided by haemodynamic parameters. Muscle relaxation was maintained with boluses of rocuronium 10–20 mg as required.

On the morning of surgery patients were randomly allocated to one of the two groups using a closed-envelope system. An anaesthetist, not directly involved in the study, prepared the infusion which consisted of four 50 ml syringes. The infusion was started 5 min after induction of anaesthesia as follows: Group R (remifentanil, n=10), remifentanil 50 $\mu g\ ml^{-1}$ at an infusion rate of 0.12 $ml\ kg^{-1}\ h^{-1}$ (equivalent to 0.1 $\mu g\ kg^{-1}\ min^{-1}$); Group S (control, n=10), normal saline 0.9% given at an infusion rate of 0.12 $ml\ kg^{-1}\ h^{-1}$.

The anaesthetist(s) in charge, the nurses on the postoperative unit and the investigator were blinded to the nature of infusion. Blood pressure and heart rate were maintained within 20% of the preoperative measurements using cardiovascular drugs at the anaesthetist's discretion. Interventions used for raising or lowering the blood pressure or heart rate were recorded. Heart rate (HR), systolic arterial blood pressure (SAP) and mean arterial pressure (MAP) were recorded from 5 min before induction of anaesthesia to 1 h after commencement of surgery, and 5 min before and every 5 min for 90 min after the end of surgery.

At the end of surgery, patients were kept sedated with propofol 100–200 $mg\ h^{-1}$, infusion of the study drug was continued and morphine 1–2 $mg\ h^{-1}$ was started. Patients were transferred to the cardiac intensive care unit (CICU). Tracheal extubation was performed when the patients were cardiovascularly stable, were normothermic (central temperature >36.5°C), were not bleeding (<50 $ml\ h^{-1}$) and had adequate spontaneous ventilation (tidal volume >7 $ml\ kg^{-1}$, $F_{I_{O_2}}$<50% and $P_{a_{CO_2}}$<6.5 kPa).

Patient age, gender, body weight, height and BMI were recorded. Duration of surgery, total duration of postoperative sedation, duration of postoperative intubation (intubation time) and total propofol infused were also recorded.

Morphine boluses were titrated by nursing staff according to VAS pain scores (if >5) or agitation (score of 2 or 3) and morphine infusion rate was continuously recorded. If pain was not controlled by morphine boluses, additional (non-opioid) analgesics were permitted. Morphine doses were noted as follows: total dose (mg) given before stopping propofol (Morphine pre-); total dose given 1 h after stopping propofol (Morphine 1 h); total dose given in first 12 h postoperatively (morphine 12 h). In addition, Morphine 1 h was subdivided into 15-min periods of morphine consumption.

Pain scores were evaluated as visual analogue scale (VAS) scores of 0–10 and recorded by the nurses at 5, 15, 30, 45, 60 min after stopping propofol and at the same intervals after extubation. Sedation scores (0–3) were recorded at 15-min intervals from the time of discontinuing propofol. An agitation score [0, patient is calm, comfortable and does not require any intervention; 1, patient is agitated and distressed, but settles with reassurance and verbal command; 2, patient is agitated and needs analgesics, mild sedation or both (one nurse could manage); 3, patient is agitated, cannot be managed by one nurse and requires heavy sedation or re-sedation or both (e.g. propofol infusion)] was recorded every 15 min for 12 h after propofol was stopped.

Data were analysed using the unpaired Student's *t*-test for parametric data, the Mann–Whitney *U*-test for non-parametric data and the χ^2-test as appropriate using SPSS version 9 software. A P-value <0.05 was considered statistically significant. Results are presented as mean (SD) or median (range).

Table 1 Patient characteristics and operative data. Group R, remifentanil; Group S, saline. Data are presented as mean (SD) or median (range). There were no significant differences between groups

	Group R (n=10)	Group S (n=10)
Age (yr)	62 (34–75)	60 (48–69)
Male/female	8/2	8/2
Weight (kg)	85.9 (18.3)	78.5 (14.3)
Height (cm)	171.5 (8)	170.5 (6.6)
Duration of surgery (min)	196 (52.7)	198 (35)
Total duration of study infusion (min)	499.4 (81)	482.7 (88)
Propofol dose (intraoperative) (mg)	1766 (517)	1967 (447)
Postoperative sedation time (min)	264 (97.4)	226 (90.7)
Extubation time (min)	575 (257)	390 (218)

Table 2 Results showing changes in heart rate (HR), systolic arterial pressure (SAP) and mean arterial pressure (MAP) before (pre-) and after (post-) stopping propofol. Data are presented as mean (SD). *P=0.06; **P=0.016

	Group R (n=10)	Group S (n=10)
No. of patients requiring drugs to stabilize haemodynamics*	2	6
HR pre-sedation (beats min^{-1})	76 (15)	72 (7)
HR post-sedation (beats min^{-1})	84 (15)	77 (8)
SAP pre-sedation (mm Hg)	125 (18)	129 (10)
SAP post-sedation (mm Hg)	143 (12)	135 (6)
MAP pre-sedation (mm Hg)	85 (12)	87 (9)
MAP post-sedation (mm Hg)**	97 (6)	89.5 (5)

Results

All 20 patients completed the study. Both groups had similar characteristics and operation data (Table 1).

There were no significant differences between haemodynamic variables in the two groups during the intraoperative period (Table 2). Two patients in Group R compared with six in Group S required pharmacological measures to stabilize arterial blood pressure and HR intraoperatively, but this was not statistically significant (P=0.06). The two patients in Group R required metaraminol to maintain their MAP within 20% of pre-induction value, whereas the six patients in Group S required isoflurane, glyceryl trinitrate (GTN) or β-blocker drugs to lower MAP within that range. Intraoperative propofol dose was 1967 (447) mg in Group S and 1766 (517) mg in Group R (P=0.18) (Table 1).

There were no significant differences in HR, MAP and SAP between the two groups before stopping sedation. In Group R, HR, MAP and SAP increased significantly after stopping sedation (P<0.05). During this period, the mean value of MAP was significantly higher in Group R (97 mm Hg) than in Group S (89.5 mm Hg) (P=0.016). No other haemodynamic variables were found to be significantly different.

There was no difference in morphine given to the two groups before stopping sedation (Table 3). Morphine requirement 1 h after stopping sedation was significantly higher in Group R (8.15 (3.59) mg) than in Group S (3.29 (2.36) mg) (P<0.01). The morphine required in the first hour was also analysed at 15-min intervals (Table 3). This showed that the maximum morphine consumption occurred in the first 30 min and was greater in Group R than in Group S (Fig. 1). There was no significant difference in total dose of morphine given to each group in the postoperative 12 h.

Table 3 Morphine consumption at different stages of the study and the worst pain and agitation scores within the first hour of stopping sedation. Morphine was given before stopping sedation (Morphine-pre), for 1 h after stopping sedation (Morphine 1 h) and for 12 h postoperatively (Morphine 12 h). Values are given as mean (SD) or median (range). Statistical significance: *P=0.009; **P=0.003; ***P=0.002; †P=0.07; ‡P=0.8

	Group R (n=10)	Group S (n=10)
Morphine pre (mg)	9.3 (2.7)	8.7 (3.5)
Morphine 1 h (mg)		
0–15 min	2.72 (2.56)	1.24 (0.97)
0–30 min*	5.35 (3.5)	1.77 (1.13)
0–45 min**	6.95 (4.1)	2.45 (1.29)
0–60 min***	8.15 (3.8)	3.3 (2.5)
Morphine 12 h (mg)	27.1 (8.7)	24 (6.6)
Pain score (VAS)†	5 (2–9)	3 (0–6)
Agitation score‡	1 (0–2)	0 (0–2)

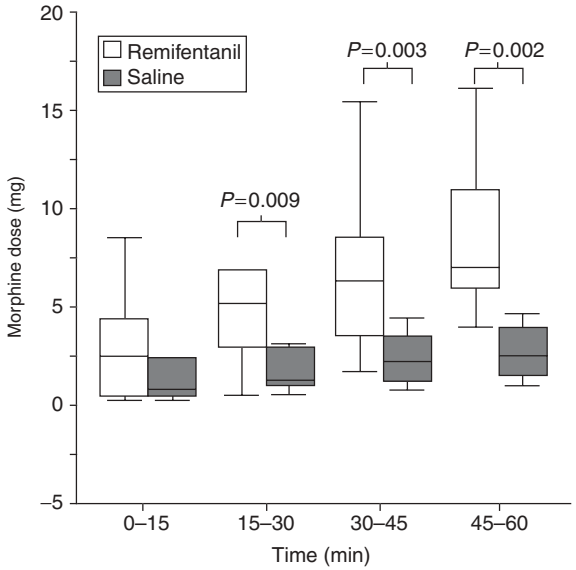

Fig 1 Cumulative doses of morphine in the first postoperative hour in the remifentanil and saline groups.

Pain scores (VAS) during the first hour after stopping sedation tended to be higher in Group R than in Group S but failed to reach statistical significance (Table 3). Sedation and agitation scores were similar in each group. Tracheal extubation times appeared greater in Group R but failed to reach statistical significance. Four patients in Group R had pain scores >5 compared with one patient in Group S (P=0.07). Three patients in Group R and one in Group S required additional (non-opioid) analgesics to supplement morphine.

Discussion

In this study we have shown that in cardiac surgery patients, additional infusion of remifentanil 0.1 μg kg^{-1} min^{-1}

following infusion of propofol for target-controlled anaesthesia and postoperative sedation for >8 h in total significantly increased the requirement for morphine in the first hour following cessation of propofol compared with a placebo group. This significant difference had disappeared 12 h after surgery. Previous studies of pain and analgesia requirements have shown differing results. This appears, in part at least, to be due to the heterogeneity of study design. For instance, Guignard and colleagues[9] studied patients undergoing major abdominal surgery, of duration >2 h, with desflurane–remifentanil anaesthesia. They compared a group receiving desflurane 0.5 minimal alveolar concentration (MAC) and variable infusion of remifentanil ($\sim$0.3 $\mu g\ kg^{-1}\ min^{-1}$) with a group receiving a fixed infusion of remifentanil 0.1 $\mu g\ kg^{-1}\ min^{-1}$ with variable desflurane concentration ($\sim$0.7 MAC). They found that the patients receiving the higher concentration of remifentanil had higher pain scores in the first 45 min, 3 h and 4 h after extubation. In addition, they found that these patients required morphine at an earlier time and had greater cumulative morphine consumption over 24 h. Cortinez and colleagues[11] studied pain and morphine requirements in patients undergoing gynaecological surgery. They found no difference in analgesic requirement during the first hour or the first 12 h postoperatively. However, it is important to note that their patients received remifentanil for <2 h.

In our study, infusion of remifentanil 0.1 $\mu g\ kg^{-1}\ min^{-1}$ for >8 h was associated with an increase in morphine requirement during the first hour but not at 12 h. This occurred despite use of fentanyl 15 $\mu g\ kg^{-1}$ at induction of anaesthesia and morphine infusion for 4 h prior to termination of remifentanil. The first hour, comparing remifentanil with placebo, has not previously been evaluated in patients receiving infusion for >2 h. This could explain why some previous studies have failed to show any difference in pain or morphine requirements. It appears that dose and duration of remifentanil are important factors in this hyperalgesia phenomenon. It may also be that the nature of surgery may affect the findings of different studies. Whether it is the duration of remifentanil infusion or the total dose that is more important in the development of hyperalgesia remains unclear. Future studies aimed at elucidating this would be useful.

Fletcher and colleagues[14] have suggested that either acute tolerance occurs during infusion or the rapid offset of the drug from the opioid receptor with the slower attachment of opioids with less affinity is the cause of the pain and agitation seen following cessation of remifentanil. In our study, a significant difference in morphine requirement was seen in the first hour but not at 12 h. Unfortunately, we did not look at times between and do not know when the effect ceased to be significant. However, it is clear from our results that most of the difference in the absolute dosages of morphine occurred between 15 and 30 min. This fits well with the relative pharmacokinetics of remifentanil and morphine (remifentanil has a context-sensitive half-life of 8 min, and onset time for i.v. morphine is about 20 min) and would provide evidence for this theory. The observation that morphine prior to cessation of remifentanil has made no difference may be due to the relative affinities of the two drugs for the μ-opioid receptor or perhaps the small doses of morphine used (8 mg over 4 h). The effect of the induction dose of fentanyl is probably minimal. Furthermore, postulated mechanisms for acute tolerance, including alterations of *N*-methyl-D-aspartate (NMDA) receptors[15] or down-regulation of opioid receptors and decoupling from the transduction system,[16 17] seem unlikely to have reversed within 1 h as would be suggested by our findings. Other studies have provided evidence to support the concept of tolerance. Vinik and Kissin[10] measured pain tolerance in volunteers given remifentanil 0.1 $\mu g\ kg^{-1}\ min^{-1}$ for 4 h. They observed that after reaching maximum analgesia in 60–90 min, the analgesic effect of remifentanil began to decline. Guignard and colleagues[9] demonstrated that increased morphine requirements persisted for 24 h after infusion of remifentanil 0.3 $\mu g\ kg^{-1}\ min^{-1}$. Neither of these observations can be explained by a simple difference in the pharmacokinetics of different opioid receptor agonists. If acute tolerance was occurring during our study we might have expected to see some difference in the remifentanil group and the placebo group before cessation of remifentanil. There was no difference in morphine dosage as a result of study design, nor were the doses of propofol between the groups different. Furthermore, the haemodynamic variables measured (HR, SAP and MAP) were not different between the two groups until after the trial infusion was stopped. It is possible that increased sympathetic activity was masked by propofol infusion. Our study has not produced any evidence to support the concept of acute tolerance.

HR and MAP were significantly higher in Group R during the first hour after stopping sedation. The increase in MAP and HR could be explained on the basis of rapid reversal of the effect of remifentanil on factors affecting the cardiovascular system. We may assume that this is due to increased sympathetic outflow in response to pain.

There was no difference in agitation score between the two groups. Although not significantly different, patients who received remifentanil had higher pain scores, despite receiving more morphine, than those in the placebo group.

Prolongation of tracheal extubation time has been previously noted.[5 18] In our study, although it took longer to extubate patients in the remifentanil group, the difference was not statistically significant (P=0.06). Significantly greater amounts of morphine given to the remifentanil group might be expected to contribute to a longer extubation time. Our results concur with those in other studies assessing 'fast-tracking' patients after various surgical procedures,[19–21] and may have clinical relevance for 'fast-tracking' patients after cardiac surgery.

We conclude that remifentanil is associated with increased analgesic requirements during the first 30 min to 1 h after

cessation following prolonged use (>8 h). This may have clinical relevance to cardiac and non-cardiac surgery patients. Therefore we suggest that studies involving analgesic requirement following prolonged remifentanil infusion should focus on this earlier period. Our study appears to provide evidence to support a pharmacokinetic explanation for the observed increased requirement for morphine. Whilst we have not demonstrated acute tolerance to remifentanil, we have not been able to reject it. The aetiology of hyperalgesia following remifentanil requires further study.

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