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Effects of maintaining a remifentanil infusion on the recovery profiles during emergence from anaesthesia and tracheal extubation

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Background. Emergence from anaesthesia and tracheal extubation can be associated with hyperdynamic circulatory responses. We examined the effects of maintaining a remifentanil infusion on recovery profiles such as coughing and cardiovascular responses after general anaesthesia.

Methods. Forty patients undergoing endoscopic sinus surgery under general anaesthesia using total i.v. anaesthesia (propofol and remifentanil) were randomly allocated to a control group ($n=20$) or remifentanil group ($n=20$) during emergence from anaesthesia. At the end of surgery, propofol was ceased and the infusion of remifentanil was stopped in the control group and maintained in the remifentanil group at a target organ concentration of 1.5 ng ml^{-1} until extubation. Heart rate (HR), mean arterial pressure (MAP), and recovery profiles were measured and evaluated.

Results. There was no significant difference in sex ratio, age, weight, height, time to eye opening, time to extubation, nausea, visual analogue scale, and time to discharge. Increases in HR and MAP occurred during emergence in the control group compared with baseline values. Increases in HR were attenuated in the remifentanil group and MAP decreased during recovery compared with baseline values. HR and MAP values were significantly higher in the control group [103 (23) beats min^{-1}, 129 (17) mm Hg] compared with the remifentanil group [79 (17) beats min^{-1}, 112 (15) mm Hg] during emergence and tracheal extubation. Moderate or severe coughing was observed only in the control group (8/20 *vs* 0/20, $P<0.001$).

Conclusions. Maintaining a remifentanil infusion reduced haemodynamic changes and coughing associated with tracheal extubation almost without significantly delaying recovery from anaesthesia.

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Emergence from anaesthesia and tracheal extubation may be associated with tracheal irritation that can cause hypertension, tachycardia, coughing, increased intracranial and intra-abdominal pressure, myocardial ischaemia, and arrhythmias.[1 2] Various strategies have been developed to prevent hyperdynamic responses and coughing during emergence, including extubation under deep anaesthesia, administration of local anaesthetics, vasodilators, and short-acting opioids.[3] Remifentanil is a potent short-acting opioid, used in total i.v. anaesthesia (TIVA) with propofol.[4] It allows rapid emergence even after a prolonged infusion.[5–7] Recent studies have reported that the use of remifentanil is beneficial in the recovery from anaesthesia.[3 8 9] We have examined whether maintaining a remifentanil infusion could have beneficial results for the patient during the recovery period. We have assessed the effects of maintaining a remifentanil infusion during emergence from anaesthesia and throughout the extubation process by evaluating recovery profiles such

as cardiovascular responses, coughing, and recovery time in a prospective randomized double-blinded manner.

Methods

After obtaining IRB approval and written informed consent, we studied 40 ASA I–II patients, aged 18–60 yr, presenting for elective endoscopic sinus surgery (ESS) between May 2008 and June 2008 in accordance with the principles of Good Clinical Practice. Exclusion criteria included a history of hypertension, asthma, and chronic obstructive lung disease, signs of a difficult airway, risk factors for perioperative aspiration, chronic coughing, and recent respiratory tract infections. Patients were allocated randomly to one of the two groups according to a computer-generated sequence of numbers until there were at least 20 patients assigned to each group.

Premedication was given with glycopyrrolate 0.2 mg i.m. Induction of anaesthesia was achieved with TIVA (propofol 4 μg ml^{-1}, remifentanil 4 ng ml^{-1} target organ concentration) via target-controlled infusion system (Orchestra Module DPS, Fresenius-Vial, Brezins, France) hidden behind a drape. When neuromuscular block was achieved with rocuronium 0.6 mg kg^{-1}, intubation was performed and anaesthesia was maintained with TIVA (Marsh model for propofol and Minto model for remifentanil, propofol 1–4 μg ml^{-1}, remifentanil 1–4 ng ml^{-1} target organ concentration). We used tracheal tubes with 7.0 mm inner diameter for women and 7.5 mm for men (Mallinckrodt Inc., St Louis, MO, USA). The cuffs were inflated with air, and cuff-pressure was monitored and maintained at 2 kPa throughout the procedure. Standard intraoperative monitoring was performed. Baseline values were obtained from the mean of three resting values in the anaesthetic room before any instrumentation. Mean arterial pressure (MAP) during surgery was controlled within 10% of resting preoperative baseline values by titrating propofol and remifentanil concentrations. No additional neuromuscular blocking agents were given.

At the end of surgery and at the start of nasal packing ('time zero'), patients assigned to the control group had both the propofol and the remifentanil infusion stopped, whereas those assigned to the remifentanil group only had propofol stopped with remifentanil maintained at a target organ concentration of 1.5 ng ml^{-1}.[8] After discontinuation of propofol, the return of neuromuscular function was confirmed using train-of-four peripheral nerve stimulation and reversal agents (pyridostigmine 0.3 mg kg^{-1}, glycopyrrolate 0.008 mg kg^{-1}) were given to all patients to prevent possible residual block. Mechanical ventilation was continued with 100% oxygen, and after 2 min, oropharyngeal suction was performed. Extubation was performed in a standard manner when patients were able to open their eyes, squeeze a hand, and lift their head on command. After tracheal extubation, remifentanil was also stopped in the remifentanil group. Eye opening time and extubation time were defined as the time between 'time zero' and eye opening or extubation,

respectively. Heart rate (HR) and MAP were recorded every 2 min from 'time zero' to 4 min after extubation. The incidence of coughing or gagging at extubation was recorded. The status of response of patients during extubation was assessed by the 5-point scale adapted from Minogue and colleagues[10] in which 1 indicates no coughing and no muscle rigidity, 2 indicates mild coughing for easy extubation, 3 indicates moderate coughing, 4 indicates severe coughing or muscle rigidity, and 5 indicates too restless to be extubated. Awakening and extubation were done by an anaesthesiologist unaware of the remifentanil infusion and the data were recorded by an investigator.

Ventilatory frequency, Sp_{O_2}, visual analogue scales (VAS; 0, as no pain, and 10, as worst possible pain), and nausea scores were measured at 15 min after arrival in the recovery unit by nurses who were blinded to the groups. Nausea scores were assessed by the 5-point scale in which 0 indicates nil nausea or vomiting, 1 indicates mild nausea without any treatment required, 2 indicates nausea that can be resolved with antiemetics, 3 indicates vomiting that can be resolved with antiemetics, and 4 indicates nausea or vomiting that does not respond to antiemetics.

A prior power analysis indicated that a minimum of 20 patients in each group were required to demonstrate a difference in MAP of 15 mm Hg or HR of 15 beats min^{-1} with a type I error of 0.05 and a power of 80%.[11]

All results are expressed as mean (SD). Categorical variables were analysed using the Mann–Whitney test and continuous variables were analysed using the *t*-test or Wilcoxon's rank sum test. HR and MAP were analysed by repeated measurement analysis. *P*-values <0.05 were considered statistically significant.

Results

Of 46 patients assessed, 40 were enrolled in the study [control group (*n* = 20); remifentanil group (*n* = 20)] and progressed through the study (Fig. 1).

There were no differences between groups in sex ratio, age, weight, height, or history of smoking. There were no significant differences in time to eye opening, time to extubation, nausea, VAS, or time to discharge. Coughing or muscle rigidity was significantly less frequent in the remifentanil group than in the control group (Table 1).

During the emergence phase, an increase in HR occurred 2 min after the end of surgery, at tracheal extubation, 2 min after tracheal extubation, and after arrival in the recovery unit, and an increase in MAP occurred at tracheal extubation in the control group compared with baseline values. In the remifentanil group, a decrease in HR and MAP occurred at the end of surgery and 2 min after the end of surgery, and an increase in HR occurred at tracheal extubation and 2 min after tracheal extubation compared with baseline values. HR and MAP values were significantly higher in the control group compared with the

remifentanil group 2 min after the end of surgery, at tracheal extubation, and 2 min after tracheal extubation. There were statistically significant differences in mean HR but no differences in mean MAP over time between the remifentanil group and the control group (P=0.001, 0.109). There were statistically significant time–group interaction effects in HR and MAP (P=0.001, 0.002) (Fig. 2).

Discussion

This study demonstrated that maintaining a remifentanil infusion during emergence and tracheal extubation minimized cardiovascular changes and improved recovery

Table 1 Patient characteristics, intraoperative anaesthetic medication requirements, and recovery profiles. Data are mean (range or SD) or n. *$P<0.001$ (by Mann–Whitney test)

	Group	
	Control (n=20)	Remifentanil (n=20)
Sex (M/F)	10/10	8/12
Age (yr)	43 (22–67)	42 (21–65)
Weight (kg)	62 (12)	66 (10)
Height (cm)	165 (9)	165 (10)
History of smoking	6	7
Total dose of propofol (mg)	646 (201)	623 (117)
Total dose of remifentanil (μg)	574 (178)	561 (120)
Time to eye opening (s)	252 (101)	288 (140)
Time to extubation (s)	363 (120)	405 (146)
Recovery status (1/2/3/4/5)	1/11/7/1/0	12/8/0/0/0*
Ventilatory frequency (bpm)	15 (2)	16 (2)
Sp_{O_2}	99 (1)	100 (1)
VAS	4.0 (1.8)	3.3 (2.3)
Nausea score (0/1/2/3/4)	17/0/3/0/0	18/2/0/0/0
Time to discharge (min)	35 (7)	38 (9)

status after TIVA with propofol and remifentanil. It has been reported that tracheal extubation causes modest and transient hypertension and tachycardia.[12] The changes in ejection fraction and cardiac work during recovery can induce undesirable complications like myocardial ischaemia in susceptible individuals.[13] Coughing frequently occurs during tracheal extubation and can cause increases in arterial pressure, HR, intracranial pressure, and intraocular pressure, and exacerbate coronary blood flow.[14 15] Smooth extubation without coughing and bucking is therefore a necessary skill for anaesthesiologists.

Various drugs such as lidocaine, esmolol, diltiazem, verapamil, and opioids have been used to attenuate these physiological changes induced by tracheal extubation.[15–17] Although there are rare reports on the influence of opioids on coughing during recovery, the administration of opioids at the end of anaesthesia is thought to reduce emergence-induced coughing. It was reported that a remifentanil bolus dose (1 μg mg^{-1}) at the end of surgery had attenuating effects on cardiovascular responses to emergence from anaesthesia and tracheal extubation; however, it had no effects on the incidence of coughing.[8] The rapid onset and short duration of action of remifentanil permits titration of the infusion rate to the response, but results in termination of analgesic effects within minutes of discontinuing the infusion. Therefore, the continuous infusion of remifentanil in our study could show better results than a bolus dose. It is common for anaesthesiologists to terminate anaesthetic agents at the end of surgery to initiate emergence. Our original idea is not to add new agents but to maintain the low-dose remifentanil infusion already being used during anaesthesia. Shajar and colleagues[8] studied the effect of a remifentanil bolus dose on the
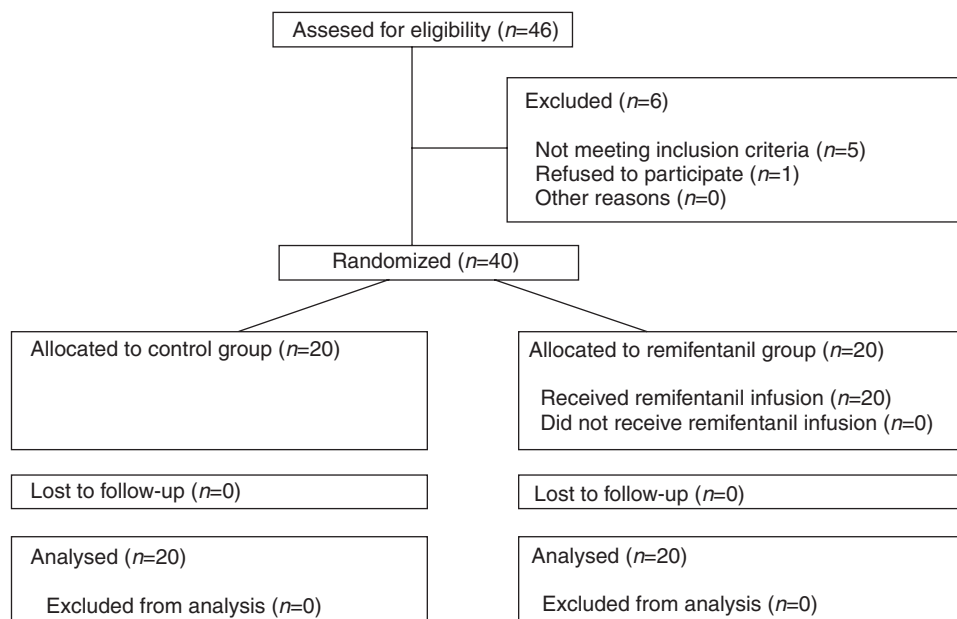

Fig 1 CONSORT diagram showing the flow of participants through each stage of a randomized trial.
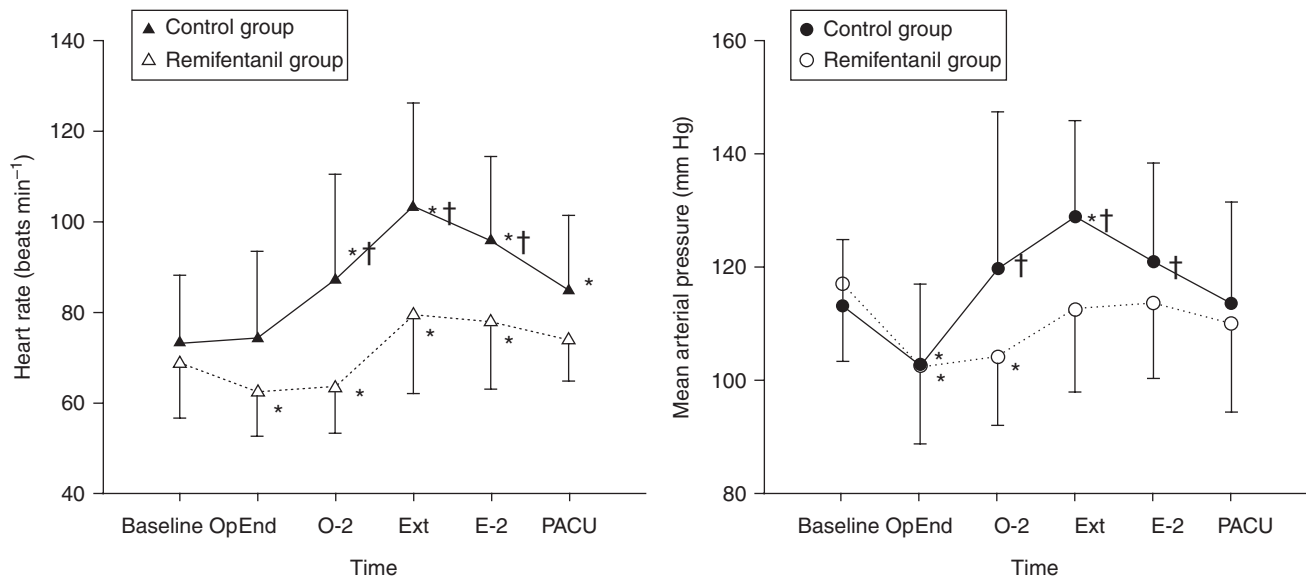
Fig 2 Haemodynamic changes during the emergence phase. Baseline, values obtained from the mean of three resting values in the anaesthetic room; Op End, at the end of surgery; O-2, 2 min after the end of surgery; Ext, at tracheal extubation; E-2, 2 min after tracheal extubation; PACU, after arrival in the post-anaesthesia care unit. Data are expressed mean (SD) (*n*=20). *P<0.05 *vs* baseline. †P<0.05 *vs* remifentanil group.

cardiovascular response during emergence. Hohlrieder and colleagues[3] discontinued the remifentanil infusion during emergence. The important difference between our study and the two previous studies is the use of the same drug (remifentanil) during emergence. Our method demonstrates how to maximize the advantages of using remifentanil during emergence in view of its pharmacokinetics.

TIVA offers the advantage of less coughing and less haemodynamic stimulation during emergence from general anaesthesia when compared with the inhalation-based technique with sevoflurane.[3] Propofol is known as a dose-dependent potent inhibitor of airway reflexes in hypnotic concentrations.[18][19] Our study shows a clear relationship between the effects of propofol and remifentanil on emergence-induced coughing. Low-dose remifentanil infusions can provide sedation, adequate respiration, and stable haemodynamics in critically ill patients; however, higher doses inhibit respiratory drive.[20] The effect-site concentration of remifentanil of $1-3$ ng ml^{-1} is known to be effective in blunting sympathetic responses to skin incision in 50% of patients when combined with other anaesthetics.[21][22] The target concentration necessary for laryngoscopy is 4 ng ml^{-1} and intraoperative requirements are in the range of $2-5$ ng ml^{-1}.[23] We thought it rational that the target concentration for smooth emergence would be <2 ng ml^{-1}, or the minimum of the usual anaesthetic maintenance dose, therefore we chose a concentration of 1.5 ng ml^{-1}. However, further studies will be required to determine the optimal dose of remifentanil during emergence from anaesthesia.

Bleeding can be aggravated by the venous congestion that accompanies coughing and bucking because of increased arterial and venous pressure and HR. Bleeding during ESS can increase complications and negatively affect the surgery and its outcome. In patients undergoing ESS, TIVA results in a better surgical field than inhalation anaesthesia.[24] A target-controlled infusion for remifentanil requires a lower dose for keeping stability in perioperative haemodynamics, compared with continuous weight-adjusted infusion.[23][25] Therefore, we chose TIVA with a target-controlled infusion as the main anaesthetic technique for this study.

In conclusion, maintaining a remifentanil infusion during emergence from anaesthesia is a simple but effective method in reducing haemodynamic changes and cough reflex activities associated with tracheal extubation with minimal effects on delaying recovery from anaesthesia.

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