

# Continuous postoperative infusion of remifentanyl inhibits the stress responses to tracheal extubation of patients under general anesthesia

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**Purpose:** The study aimed to assess the combined effects of parecoxib with three different doses of remifentanyl and its effect on the stress and cough responses following tracheal extubation under general anesthesia.

**Methods:** A total of 120 patients with American Society of Anesthesiologists (ASA) scores of I or II, undergoing selective thyroidectomy with total intravenous anesthesia (propofol-remifentanyl) and tracheal intubation, were randomly allocated to be treated with an intravenous injection of parecoxib and a continuous infusion of remifentanyl at 0.1  $\mu\text{g/kg/min}$  (R1), 0.2  $\mu\text{g/kg/min}$  (R2), 0.3  $\mu\text{g/kg/min}$  (R3), or an isotonic saline injection (the control group). Hemodynamic vital signs, emergence time, extubation time, sedation-agitation scale (SAS) score, pain visual analog scale (VAS) score, occurrence of coughing, and side effects were recorded before surgery and during the peri-extubation period. The vital signs included blood pressure (BP), heart rate (HR), respiratory rate (R), and peripheral arterial oxygen saturation ( $\text{SPO}_2$ ).

**Results:** BP, HR, the occurrence rate of coughing, and extubation awareness decreased with the dose of remifentanyl, and the differences among the groups were significant ( $P < 0.05$ ). Emergence and extubation time increased with the dose of remifentanyl, and the differences among the groups were significant ( $P < 0.05$ ). The occurrence rates of respiratory depression and bradycardia in group R3 were significantly higher than those in other groups ( $P < 0.05$ ). SAS and VAS were lowest in group R3, and the differences among the groups were significant ( $P < 0.05$ ). BP, HR, SAS, and VAS increased with time in the remifentanyl groups.

**Conclusion:** The combined use of parecoxib and a moderate dose of remifentanyl can effectively suppress the stress and coughing responses during the peri-extubation period. The appropriate quantity of remifentanyl was found to be 0.2  $\mu\text{g/kg/min}$ , as this dosage caused no side effects.

**Keywords:** remifentanyl, continuous infusion, stress response, coughing, tracheal extubation, anesthesia

## Introduction

Tracheal extubation is commonly performed during the emergence phase after stopping anesthetics. Significant systemic stress responses to pain and airway stimulation can occur during this period, including agitation and cough, which may cause hypertension, tachycardia, and increased intracranial hypertension.<sup>1</sup> This not only greatly increases the discomfort of patients but it also increases the rates of angiocardiopathy and other side effects. Gacouin et al<sup>2</sup> evaluated 203 patients' pain using a visual analog scale (VAS), and they found >73% of patients experienced moderate or severe pain during extubation. Traditionally, anesthetic withdrawal involves discontinuing both propofol and remifentanyl, which can result in pain experienced by patients in an unawakened state and which can lead to a stress response induced by the tracheal catheter. This

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<http://dx.doi.org/10.2147/JPR.S123423>

Journal of Pain Research 2017:10 933–939



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widely increases the probability of dysphoria and adverse reactions during the peri-extubation period. Therefore, it is extremely important to identify a method to effectively reduce the stress response during peri-extubation.

Remifentanyl is a new ultra-short-acting opioid  $\mu$ -receptor stimulant, with rapid onset and offset activity, which can also be rapidly hydrolyzed in tissue and blood with no dependence on liver and kidney function.<sup>3</sup> Continuous infusion of remifentanyl has no prolonged context-sensitive half-time or cumulative effects,<sup>4</sup> which makes it easier to maintain a stable concentration at the effect site. Therefore, remifentanyl is widely used for clinical anesthesia.<sup>5</sup> Remifentanyl not only has an anesthetic and analgesic effect but it can also reduce the incidence of respiratory depression and other adverse reactions. The use of a continuous infusion of remifentanyl after total intravenous anesthesia has multiple advantages, as remifentanyl can be used to control excessive stress responses.<sup>6</sup> Aouad et al<sup>7</sup> showed that the use of a small dose of remifentanyl did not prolong the time taken to wake up from anesthesia, and it decreased the occurrence of cough during the emergence phase.

As a previous study showed, the use of remifentanyl often results in postoperative discomfort and hyperalgesia.<sup>8</sup> Therefore, a long-acting postoperative analgesic is of urgent need to avoid postoperative hyperalgesia and pain caused by remifentanyl. Parecoxib is a new nonsteroidal anti-inflammatory drug (NSAID) that has selective cyclooxygenase-2 inhibitory activity, strong anti-inflammatory analgesic activity, long-term efficacy,<sup>8</sup> and minimal cardiovascular risk.<sup>9</sup> Many studies have shown that NSAIDs can ameliorate the side effects caused by opioids, including respiratory depression, nausea, emesis, and somnolence,<sup>10</sup> so parecoxib is often used as a postoperative analgesic.

Until now, the appropriate dose of remifentanyl for inhibiting stress responses has remained unclear. The stress response that occurs during major surgeries is not only related to the irritation caused by the endotracheal tube but also to the surgical stimulation of patients during the emergence phase. Therefore, this study aimed to explore the combined effect of parecoxib with different doses of remifentanyl on hemodynamic vital signs and stress responses to extubation.

## Patients and methods

### Patients

We obtained approval from the institutional review board of the First Affiliated Hospital of Kunming Medical University, People's Republic of China, and written informed consent from the patients. A total of 120 patients with American Society of Anesthesiologists scores of I or II, who were

20–50 years old and weighed 40–75 kg, were selected to take part in the study, which involved elective thyroidectomy with general anesthesia and tracheal intubation. Patients with the following characteristics were excluded from the study: patients with an allergy to opioids or NSAIDs, hypertension, a history of ischemic heart disease, or a history of cerebrovascular disease. The included patients were randomly divided into four groups with 30 patients per group: control group, low-dose remifentanyl group (R1), medium-dose remifentanyl group (R2), and high-dose remifentanyl group (R3).

### Procedure

After entering the operating room, the blood pressure (BP), heart rate (HR), respiratory rate (R), and peripheral arterial oxygen saturation ( $\text{SPO}_2$ ) of each patient were routinely monitored. The venous channel was opened and an isotonic saline solution (10 ml/kg/h) was administered. After the patient reached a stable condition, anesthesia induction was performed. For the patients in all four groups, this involved the intravenous infusion of fentanyl (4  $\mu\text{g/kg}$ ), rocuronium bromide (0.6 mg/kg), and propofol (2.5 mg/kg).

Then anesthesia was maintained using a venous perfusion of propofol (6–12 mg/kg/h) and remifentanyl (0.1–0.5  $\mu\text{g/kg/min}$ ) before the incision suture. The doses were changed according to each patient's response. When suturing the incision, the patients in all four groups received an intravenous infusion of parecoxib (40 mg) and an intravenous drip of tropisetron (4 mg). The patients in the control group received an isotonic saline injection (instead of propofol and remifentanyl). In contrast, the patients in groups R1, R2, and R3 were treated with intravenous remifentanyl at 0.1  $\mu\text{g/kg/min}$ , 0.2  $\mu\text{g/kg/min}$ , and 0.3  $\mu\text{g/kg/min}$ , respectively.

After the operation, the patients' responses to commands were monitored every 2 min. Patients who could open their eyes on command and responded to commands were assessed as being conscious. Extubation and discontinuation of remifentanyl were initiated when the patients had the following conditions: response to commands, spontaneous respiration, deglutition reflex, tidal volume  $>8$  ml/kg, respiratory rate  $>10$  times/min, and  $\text{SPO}_2 >95\%$ .

### Observation indexes

The BP, HR, R, and  $\text{SPO}_2$  of each patient were monitored before anesthesia induction (at baseline), and these indexes were also monitored when the patient was in a waking state, at extubation, and at 2, 5, 10, and 15 min after extubation. The emergence time was defined as the time between discontinuation of propofol and the point at which the patient

regained consciousness. The extubation time was defined as time between the discontinuation of propofol and extubation. The operation, emergence, and extubation times of each patient were recorded. The times and severity of cough during the extubation time were recorded. Anesthesia-, extubation-, and remifentanyl-related adverse reactions were also recorded, which included intraoperative awareness, comfort level during extubation, cough, laryngospasm, encephalalgia, dizziness, nausea, emesis, uroschesis, and skin pruritus. Furthermore, the sedation-agitation scale (SAS; 1 = unarousable; 7 = dangerous agitation)<sup>11</sup> and the pain VAS at 0 min (i.e., the time at which the patient regained consciousness), and 5, 10, and 15 min after recovery of consciousness, were recorded to evaluate the patients' sedation levels.

## Statistical analysis

Statistical analyses were performed using SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA). The qualitative data are presented as frequencies (with percentages), and comparison among the groups was performed using chi-square tests with  $\alpha = 0.05$ . A normality test was carried out for each quantitative variable. The normally distributed data are presented as mean  $\pm$  standard deviation, and comparison among the groups was performed using one-way analysis of variance (ANOVA). The non-normally distributed data are presented as medians (with ranges), and comparison among the groups was performed using nonparametric tests. Repeated-measures analyses of the effects of the different

treatments and times on the SAS and VAS scores were performed using generalized estimating equations (GEEs). We selected  $\alpha = 0.05$  as the standard level of significance and so  $P < 0.05$  was considered statistically significant.

## Results

In this study, 120 patients were selected and there were 30 patients in each group. As shown, gender, age, surgical time, nausea, emesis, dizziness, headache, intraoperative awareness, and uroschesis in the control, R1, R2, and R3 groups were not significantly different (Table 1). The emergence and extubation times were different among the groups, with increases in remifentanyl dose, and considerably longer times in group R2 (remifentanyl at 0.2  $\mu\text{g/kg/min}$ ) and group R3 (remifentanyl at 0.3  $\mu\text{g/kg/min}$ ) compared to the time in group R1 (remifentanyl at 0.1  $\mu\text{g/kg/min}$ ) and control group ( $P < 0.05$ ). The number of patients with a cough in each group decreased with remifentanyl dose, and the differences were significant (21 in the control group, 18 in group R1, 8 in group R2, and 3 in group R3,  $P = 0.000$ ). The number of patients with respiratory depression was higher in the group with the highest dose of remifentanyl (1 in groups R1 and R2 and 7 in group R3,  $P = 0.002$ ). The number of patients in each group unknown about the extubation increased with the remifentanyl dose, and all the patients in groups R2 and R3 knew about extubation (14, 25, 30, and 30 in the control, R1, R2, and R3 groups, respectively,  $P = 0.000$ ). Only 10% of patients in group R3 had bradycardia and 9% of patients

**Table 1** Comparison of patient characteristics and postoperative complications

Variable	Group C	Group R1	Group R2	Group R3	P
Gender, n (%)					0.065
Male	3 (10.0%)	10 (33.3%)	11 (36.7%)	6 (20.0%)	–
Female	27 (90.0%)	20 (66.7%)	19 (63.3%)	24 (80.0%)	–
Age, mean $\pm$ SD	40.47 $\pm$ 11.65 <sup>a</sup>	43.6 $\pm$ 12.24 <sup>a</sup>	42.1 $\pm$ 12.44 <sup>a</sup>	37.53 $\pm$ 11.13 <sup>a</sup>	0.236
BMI, median (range)	21.92 (17.99, 25.97) <sup>a</sup>	22.72 (16.61, 30.45) <sup>a</sup>	23.83 (17.97, 29.76) <sup>a</sup>	22.1 (17.69, 29.52) <sup>a</sup>	0.046
Surgical time (min), median (range)	115 (60, 215)	107.5 (50, 240)	122.5 (45, 315)	125 (70, 210)	0.264
Emergence time (min), median (range)	12 (6, 23) <sup>a</sup>	15 (6, 30) <sup>a,c</sup>	20 (14, 30) <sup>b,c</sup>	25.5 (15, 45) <sup>b</sup>	0.000
Extubation time (min), median (range)	16 (16, 16) <sup>a</sup>	18 (8, 35) <sup>a,c</sup>	23 (9, 36) <sup>b,c</sup>	31.5 (17, 47) <sup>b</sup>	0.000
Cough, n (%)	21 (70.0%) <sup>a</sup>	18 (60.0%) <sup>a</sup>	8 (27.7%) <sup>b</sup>	3 (10.0%) <sup>b</sup>	0.000
Respiratory depression, n (%)	0 <sup>a</sup>	1 (3.3%) <sup>a,b</sup>	1 (3.3%) <sup>a,b</sup>	7 (23.3%) <sup>b</sup>	0.002
Bradycardia, n (%)	0 <sup>a</sup>	0 <sup>a</sup>	0 <sup>a</sup>	3 (10.0%) <sup>a</sup>	0.027
Muscle rigidity, n (%)	0	0	0	0	–
Nausea and emesis, n (%)	14 (48.3%)	8 (27.7%)	11 (36.7%)	10 (33.3%)	0.144
Dizziness headache, n (%)	10 (33.3%)	11 (36.7%)	9 (30.0%)	6 (20.7%)	0.244
Intraoperative awareness, n (%)	1 (3.3%)	1 (3.3%)	2 (6.9%)	0	0.659
Uroschesis, n (%)	4 (13.3%)	5 (16.7%)	2 (6.7%)	1 (3.3%)	0.104
Unknown about extubation, n (%)	14 (46.7%) <sup>a</sup>	25 (83.3%) <sup>b</sup>	30 (100%) <sup>b</sup>	30 (100%) <sup>b</sup>	0.000
Awareness with comfort, n (%)	4 (13.3%) <sup>a</sup>	3 (10.0%) <sup>a</sup>	0 <sup>a</sup>	0 <sup>a</sup>	0.009
Tolerable discomfort, n (%)	4 (13.3%) <sup>a</sup>	3 (10.0%) <sup>a</sup>	0 <sup>a</sup>	0 <sup>a</sup>	0.009
Intolerable discomfort, n (%)	9 (30.0%) <sup>a</sup>	0 <sup>b</sup>	0 <sup>b</sup>	0 <sup>b</sup>	0.000

**Notes:**  $P < 0.05$  is considered as statistically significant. <sup>a-c</sup>The results of two comparisons; no significant statistical difference between two groups with same letter, but significant statistical differences between two groups with different letters.

**Abbreviations:** BMI, body mass index; C, sodium chloride; R1, remifentanyl (0.1  $\mu\text{g/kg/min}$ ); R2, remifentanyl (0.2  $\mu\text{g/kg/min}$ ); R3, remifentanyl (0.3  $\mu\text{g/kg/min}$ ).

in the control group experienced intolerable discomfort with extubation. A small number of patients in the control and low-dose remifentanyl groups were aware but did not experience discomfort (13.3%) or experienced tolerable discomfort (10%) (Table 1). These results indicated that continuous postoperative infusion of remifentanyl can not only reduce coughing and discomfort responses to extubation but they can also increase respiratory depression and bradycardia.

The SAS and VAS scores of the patients in each group were recorded at emergence time (0 min) and at 5, 10, and 15 min after emergence. These data were analyzed using GEEs, and the results are shown in Tables 2–5, respectively. There were significant differences in the SAS scores among the groups (Wald  $\chi^2 = 17.986$ ,  $P = 0.000$ ), and the odds ratios (ORs) of groups R1, R2, and R3 were 0.163, 0.246, and 0.887, respectively, compared with the control group, indicating that the SAS score decreased with the remifentanyl dose. The

**Table 2** Number (percentage) of SAS

Emergence time	Score	Group C, n (%)	Group R1, n (%)	Group R2, n (%)	Group R3, n (%)
0 min	3	19 (63.3%)	6 (20%)	9 (30%)	16 (53.3%)
	4	11 (36.7%)	24 (80%)	21 (70%)	14 (46.7%)
5 min	3	1 (3.3%)	0	0	0
	4	19 (63.3%)	9 (30%)	11 (37.9%)	24 (80%)
	5	10 (33.3%)	21 (70%)	18 (62.1%)	6 (20%)
10 min	4	1 (3.3%)	1 (3.3%)	0	0
	5	29 (96.7%)	29 (96.7%)	30 (100%)	30 (100%)
15 min	4	1 (3.3%)	0	0	0
	5	29 (96.7%)	28 (96.6%)	30 (100%)	30 (100%)
	6	0	1 (3.4%)	0	0

**Abbreviations:** C, sodium chloride; R1, remifentanyl (0.1  $\mu\text{g/kg/min}$ ); R2, remifentanyl (0.2  $\mu\text{g/kg/min}$ ); R3, remifentanyl (0.3  $\mu\text{g/kg/min}$ ); SAS, sedation-agitation scale.

**Table 3** Correlation between SAS and the dose and infusion time of remifentanyl

Parameters	B	OR	95%CI of OR		Hypothesis test		
			Lower	Upper	Wald $\chi^2$	df	P
SAS = 6.00	-17.197	0.000	0.000	0.000	114.564	1	0.000
SAS = 5.00	-6.508	0.001	0.000	0.011	40.884	1	0.000
SAS = 4.00	-4.456	0.634	0.292	1.375	1.332	1	0.248
Group = R3	-1.120	0.887	0.335	2.351	0.058	1	0.810
Group = R2	-1.404	0.246	0.090	0.674	7.436	1	0.006
Group = R1	-1.813	0.163	0.053	0.503	9.965	1	0.002
Group = C	0 <sup>a</sup>						
Time = 15min	-11.020	0.000	0.000	0.000	52.850	1	0.000
Time = 10min	-9.904	0.000	0.000	0.001	69.864	1	0.000
Time = 5min	-5.489	0.004	0.001	0.030	29.826	1	0.000
Time = 0min	0 <sup>a</sup>						

**Note:** <sup>a</sup>reference.

**Abbreviations:** C, sodium chloride; R1, remifentanyl (0.1  $\mu\text{g/kg/min}$ ); R2, remifentanyl (0.2  $\mu\text{g/kg/min}$ ); R3, remifentanyl (0.3  $\mu\text{g/kg/min}$ ); SAS, sedation-agitation scale; CI, confidence interval; B, regression coefficient; OR, odds ratio; df, degrees of freedom.

**Table 4** Number (percentage) of VAS

Emergence time	Score	Group C, n (%)	Group R1, n (%)	Group R2, n (%)	Group R3, n (%)
0 min	0	25 (83.3%)	29 (96.7%)	29 (96.7%)	30 (100%)
	1	3 (10%)	1 (3.3%)	0	0
	2	2 (6.7%)	0	1 (3.3%)	0
5 min	0	3 (10%)	20 (66.7%)	13 (43.3%)	16 (53.3%)
	1	9 (30%)	8 (26.7%)	11 (36.7%)	12 (40%)
	2	13 (43.3%)	2 (6.7%)	3 (10%)	2 (6.7%)
	3	5 (16.7%)	0	2 (6.7%)	0
	5	0	0	1 (3.3%)	0
10 min	0	1 (3.3%)	7 (24.1%)	8 (26.7%)	3 (10%)
	1	1 (3.3%)	14 (48.3%)	7 (23.3%)	13 (43.3%)
	2	17 (56.7%)	8 (27.6%)	9 (30%)	11 (36.7%)
	3	11 (36.7%)	0	4 (13.3%)	3 (10%)
	5	0	0	2 (6.7%)	0
15 min	0	1 (3.3%)	1 (3.3%)	3 (10%)	1 (3.3%)
	1	1 (3.3%)	7 (23.3%)	6 (20%)	4 (13.3%)
	2	9 (30%)	17 (56.7%)	12 (40%)	16 (53.3%)
	3	16 (53.3%)	5 (16.7%)	5 (16.7%)	6 (20%)
	4	3 (10%)	0	3 (10%)	3 (10%)
	5	0	0	1 (3.3%)	0

**Abbreviations:** C, sodium chloride; R1, remifentanyl (0.1  $\mu\text{g/kg/min}$ ); R2, remifentanyl (0.2  $\mu\text{g/kg/min}$ ); R3, remifentanyl (0.3  $\mu\text{g/kg/min}$ ); VAS, visual analog scale.

**Table 5** Correlation between VAS and the dose and infusion time of remifentanyl

Parameters	B	OR	95%CI of OR		Hypothesis test		
			Lower	Upper	Wald $\chi^2$	df	P
VAS = 5.00	-8.913	0.000	0.000	0.001	94.411	1	0.000
VAS = 4.00	-7.680	0.000	0.000	0.002	136.422	1	0.000
VAS = 3.00	-5.494	0.004	0.001	0.013	87.361	1	0.000
VAS = 2.00	-3.334	0.036	0.014	0.094	45.798	1	0.000
VAS = 1.00	-1.689	0.185	0.079	0.430	15.304	1	0.000
Group = R3	1.765	5.844	2.635	12.961	18.877	1	0.000
Group = R2	1.645	5.183	1.990	13.503	11.346	1	0.001
Group = R1	2.332	10.298	4.479	23.677	30.135	1	0.000
Group = C	0 <sup>a</sup>						
Time = 15 min	-6.280	0.002	0.001	0.006	122.796	1	0.000
Time = 10 min	-5.010	0.007	0.003	0.017	106.487	1	0.000
Time = 5 min	-3.489	0.031	0.014	0.069	70.966	1	0.000
Time = 0 min	0 <sup>a</sup>						

**Note:** <sup>a</sup>reference.

**Abbreviations:** C, sodium chloride; R1, remifentanyl (0.1  $\mu\text{g/kg/min}$ ); R2, remifentanyl (0.2  $\mu\text{g/kg/min}$ ); R3, remifentanyl (0.3  $\mu\text{g/kg/min}$ ); B, regression coefficient; OR, odds ratio; CI, confidence interval; VAS, visual analog scale; df, degrees of freedom.

SAS scores at different times were also statistically different (Wald  $\chi^2 = 74.983$ ,  $P = 0.000$ ), and the ORs at 5, 10, and 15 min were 0.004, 0.000, and 0.000, respectively, compared with at 0 min, indicating that the SAS scores increased with time after emergence. Furthermore, the VAS score analysis showed that the VAS score was associated with the remifentanyl dose (Wald  $\chi^2 = 32.668$ ,  $P = 0.000$ ) and time (Wald  $\chi^2 = 142.554$ ,  $P = 0.000$ ). The VAS score was highest in group R1 (OR = 10.298, 5.183, and 5.844 in groups R1, R2, and R3, respectively) and it increased with time (OR = 0.031, 0.007, and 0.002 at 5, 10, and 15 min, respectively).

The cardiovascular vital signs (systolic and diastolic BP, HR, R, and  $\text{SPO}_2$ ) of the patients in each group were monitored at baseline, emergence, extubation, and 2, 5, 10, and 15 min after extubation. Compared with baseline, the systolic and diastolic BP, HR, and  $\text{SPO}_2$  in the control group all clearly increased at emergence, extubation, and after extubation ( $P < 0.05$ ), but R was significantly reduced at emergence, extubation, and after extubation ( $P < 0.05$ ). In the R1 group, the diastolic BP decreased only 5 min after extubation ( $P < 0.05$ ) and HR dramatically increased at extubation ( $P < 0.05$ ). Systolic and diastolic BP decreased at emergence in the R2 and R3 groups ( $P < 0.05$ ). HR increased 5 min after extubation in the R2 group ( $P < 0.05$ ), and it decreased at emergence but increased at 5, 10, and 15 min after extubation in the R3 group ( $P < 0.05$ ). The R and  $\text{SPO}_2$  decreased and increased, respectively, in the R1, R2, and R3 groups ( $P < 0.05$ ). Compared with the control group, the systolic and diastolic BP in the remifentanyl groups was significantly lower at emergence, extubation, and 2 and 5 min after extubation ( $P < 0.05$ ). The HR of the remifentanyl groups greatly decreased at emergence, extubation, and 2 min after extubation ( $P < 0.05$ ). The  $\text{SPO}_2$  of the remifentanyl groups showed no significant change (Table 6). These results suggest that postoperative remifentanyl infusions can decrease the rise in systolic and diastolic BP, HR, and R at emergence and extubation, and they showed that the effect of a high dose of remifentanyl on these variables was longer and better.

## Discussion

Many studies have been carried out to explore the methods that can effectively alleviate stress responses, agitation, and discomfort due to tracheal extubation during the emergence time from general anesthesia. Vasoactive drugs, such as esmolol and ebrantil, can be used to inhibit cardiovascular responses to tracheal extubation. However, they can only improve tachycardia and hyperpnea, and fail to inhibit the intense stimulation of the trachea by the tracheal catheter and to effectively stop the agitation and discomfort during the peri-extubation period.<sup>12</sup> Long-acting opioid analgesics, such as fentanyl, sufentanyl, and dezocine, have been used during the peri-extubation period to inhibit stress responses and discomfort, and they have been shown to have some effect. However, the controllability of long-acting opioid analgesics is poor due to longer elimination half-life and prolonged context-sensitive half-life. The use of fentanyl can not only reduce stress responses but it can also induce respiratory depression and delay recovery.<sup>13</sup>

Remifentanyl is a new kind of ultra-short-acting opioid analgesic. It has many advantages such as rapid onset, shorter elimination half-life, no accumulation after long-term application, no effect caused by impaired hepatorenal function, and

no prolonged context-sensitive half-life.<sup>14,15</sup> Therefore, remifentanyl may be the most easily controllable opioid analgesic. In our study, continuous injection of remifentanyl after surgery decreased the number of patients with coughs and increased the patients' comfort during emergence from general anesthesia and extubation, though it also prolonged the emergence and extubation times. Furthermore, the patients treated with remifentanyl had no significant adverse effects such as nausea, emesis, dizziness, headache, or uroschisis. The occurrence rates of cough and discomfort were effectively reduced, and there was no obvious occurrence of respiratory depression or bradycardia among the patients treated with remifentanyl at 0.2  $\mu\text{g}/\text{kg}/\text{min}$  after surgery. The fact that continuous injection of remifentanyl after surgery can inhibit airway reflex and attenuate the stimulus of tracheal tube may account for the result.<sup>7,16</sup>

Previous research has suggested that remifentanyl does not cause a decrease in the bispectral index value,<sup>17</sup> which may be inversely correlated with the level of analgesia.<sup>18</sup> The SAS and VAS results in this study showed that the sedative and analgesic effects were enhanced by increased doses of remifentanyl, indicating that continuous postoperative infusion of remifentanyl can effectively relieve postoperative pain.<sup>19</sup> In addition, the analysis of hemodynamic vital signs showed that continuous postoperative infusion of remifentanyl inhibited the elevation of systolic and diastolic BP during the peri-extubation period and that using a high dose of remifentanyl (0.3  $\mu\text{g}/\text{kg}/\text{min}$ ) delayed the rise in HR. This demonstrates that the postoperative use of a low dose of remifentanyl can ameliorate any changes in BP and HR during the peri-extubation period, and it has beneficial effects on hemodynamic stability.<sup>20</sup> However, the sedative and analgesic effects and hemodynamic stability were not only enhanced with the dose of remifentanyl, but they also reduced with time, which suggests that the comfort of patients during the peri-extubation period was associated with the remifentanyl dose<sup>21</sup> and its short time of offset.<sup>22</sup> Moreover, the slight changes in BP and HR caused by remifentanyl can return to their original levels within 5–10 min without treatment.<sup>23</sup>

## Conclusion

In our study, we showed that continuous infusion of remifentanyl during peri-extubation period can effectively suppress stress and coughing responses and improve patients' comfort during the emergence phase. Furthermore, use of remifentanyl at 0.2  $\mu\text{g}/\text{kg}/\text{min}$  reduced the rate of side effects compared to that at 0.3  $\mu\text{g}/\text{kg}/\text{min}$ , and it may be appropriate for inhibiting stress responses to tracheal extubation under general anesthesia. Therefore, continuous postoperative infusion of remifentanyl at a dose of 0.2  $\mu\text{g}/\text{kg}/\text{min}$  may be safe and comfort for tracheal extubation.



**Table 6** Comparison of SBP, DBP, HR, R, and SPO<sub>2</sub> before surgery, emergence, extubation, and at 2, 5, 10, and 15 min after extubation

Parameters		SBP (mmHg)	DBP (mmHg)	HR (beats/min)	R (beats/min)	SPO <sub>2</sub>
Group C	Before surgery (baseline)	120.33 ± 12.72	70.53 ± 9.84	77.73 ± 8.7	17.57 ± 0.97	95.6 ± 1.45
	Emergence	142.87 ± 16.35**	85.3 ± 11.92**	93.6 ± 10.91**	12.57 ± 0.82**	100 ± 0**
	Extubation	146.9 ± 16.05**	86.7 ± 11.05**	97.97 ± 12**	13.17 ± 0.7**	100 ± 0**
	2 min after extubation	142.33 ± 13.63**	82.8 ± 11.12**	94.2 ± 11.13**	14.67 ± 0.71**	100 ± 0**
	5 min after extubation	135.4 ± 13.02**	80.3 ± 10.22**	91.2 ± 9.91**	15.73 ± 0.58**	100 ± 0**
	10 min after extubation	130.47 ± 11.99**	75.8 ± 9.71**	86.67 ± 9.77**	16.73 ± 0.74**	100 ± 0**
	15 min after extubation	129.1 ± 13.18**	74.5 ± 10.58**	85.77 ± 9.88**	17.13 ± 0.82*	100 ± 0**
Group R1	Before surgery (baseline)	126.93 ± 13.97	77.77 ± 10.36††	77.03 ± 11.79	17.77 ± 0.94	94.87 ± 2.24
	Emergence	121.8 ± 16.27††	72.57 ± 11.12**††	78.63 ± 14.12††	11.67 ± 1.06**††	100 ± 0**
	Extubation	127.43 ± 16.5††	76.17 ± 11.36††	84.73 ± 13.71**††	12.9 ± 0.88**	100 ± 0**
	2 min after extubation	129.43 ± 16.04††	76.83 ± 11.55†	83 ± 13.11**††	14.27 ± 0.74**††	100 ± 0**
	5 min after extubation	127.77 ± 13.78†	73.67 ± 11.33**††	82.7 ± 10.61**††	15.6 ± 0.77**	100 ± 0**
	10 min after extubation	127.37 ± 17.98	76 ± 13.67	85.27 ± 11.28**	16.63 ± 0.72**	99.97 ± 0.18**
	15 min after extubation	129.77 ± 18.57	75.1 ± 13.78	84.73 ± 10.83**	17.37 ± 0.56**	100 ± 0**
Group R2	Before surgery (baseline)	126.27 ± 14.48	77.93 ± 12.46†	79.13 ± 11.2	17.37 ± 0.96	95.33 ± 1.83
	Emergence	118.1 ± 14.21**††	69.43 ± 10.62**††	75.77 ± 13.78††	12.33 ± 1.35**	100 ± 0**
	Extubation	124.77 ± 17.18††	73.97 ± 11.87††	81 ± 15.3††	13.1 ± 1.16**	99.9 ± 0.4**
	2 min after extubation	123.8 ± 15.7††	74.2 ± 12.1††	82.47 ± 15.44††	14.41 ± 0.95**	99.87 ± 0.57**
	5 min after extubation	126.2 ± 18.14†	74.3 ± 12.83†	85.4 ± 14.43**	15.37 ± 0.67**††	99.83 ± 0.65**
	10 min after extubation	127.83 ± 17.63	79.37 ± 12.55	85.87 ± 14.62**	16.5 ± 0.82**	99.8 ± 0.81**
	15 min after extubation	130.77 ± 16.86	78.83 ± 12.45	85.47 ± 14.99*	17.13 ± 0.73	99.83 ± 0.65**
Group R3	Before surgery (baseline)	121.4 ± 12.84	71.8 ± 11.93	77.6 ± 10.29	17.9 ± 0.55	95.9 ± 1.45
	Emergence	114.03 ± 11.77**††	65.8 ± 8.46**††	71.73 ± 13.98**††	11.53 ± 1.25**††	99.97 ± 0.18**
	Extubation	118.5 ± 13.02††	70.8 ± 8.96††	79.23 ± 14.14††	12.63 ± 1**††	100 ± 0**
	2 min after extubation	121.37 ± 11.61††	70.33 ± 10.6††	78.87 ± 13.91††	14 ± 0.91**††	100 ± 0**
	5 min after extubation	120.3 ± 10.68††	73 ± 9.61††	82.23 ± 13.58**††	15.03 ± 0.81**††	99.9 ± 0.4**
	10 min after extubation	120.23 ± 8.91††	73.1 ± 8.03	82.7 ± 13.47*	16.37 ± 0.61**††	99.97 ± 0.18**
	15 min after extubation	121.47 ± 8.54†	74.13 ± 8.65	82.07 ± 12.71*	17.33 ± 1.06**	99.97 ± 0.18**

**Notes:** \**P* < 0.05, \*\**P* < 0.01 vs before surgery within-group, †*P* < 0.05, ††*P* < 0.01 vs group C.

**Abbreviations:** SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; R, respiratory rate; SPO<sub>2</sub>, saturation of pulse oximetry; C, sodium chloride; R1, remifentanyl (0.1 µg/kg/min); R2, remifentanyl (0.2 µg/kg/min); R3, remifentanyl (0.3 µg/kg/min).

## Author contributions

JS substantially contributed to the conception and design of this study; GZ, XY, and YL substantially contributed to the acquisition of data, or analysis and interpretation of data; GZ and XY wrote the manuscript; JS revised it

critically for important intellectual content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed toward data analysis, drafting

and revising the paper and agree to be accountable for all aspects of the work.

All authors have given the final approval of the version to be published.

## Disclosure

The authors report no conflicts of interest in this work.

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