Remifentanil can prevent the withdrawal movements due to the intravenous injection of rocuronium

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Byung-In Choi is approved

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December 2006
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ABSTRACT

Remifentanil can prevent the withdrawal movements due to the intravenous injection of rocuronium

Background. There are high incidences of pain and pain induced withdrawal movements due to the intravenous injection of rocuronium. This study was conducted to evaluate the effect of pretreatment of remifentanil on the withdrawal movements due to the intravenous injection of rocuronium during the anesthetic induction.

Methods. Ninety adults female patients undergoing thyroidectomy with general anesthesia were allocated to three Groups by double blind randomization. Each patient received one of three solutions of equal volume of 4 ml through a 20G intravenous cannula inserted into the forearm cephalic vein over 30 seconds: normal saline (N/S) (Group I, n=30, control), remifentanil 0.5 µg/kg in N/S (Group II, n=30) or remifentanil 1 µg/kg (Group III, n=30) in N/S. Thirty seconds after remifentanil administration, anesthesia was induced with IV thiopental 5 mg/kg at the injection rate of 0.5 ml/sec. Twenty seconds after thiopental injection, IV rocuronium 0.6 mg/kg was administered at the injection rate of 0.5 ml/sec and patients’ withdrawal movements were assessed. Mean arterial pressure and heart rate before and during the anesthetic induction were measured to clarify the effect of remifentanil on the cardiovascular response following by laryngoscopy and endotracheal intubation.

Results. The incidence of withdrawal movements was significantly reduced in both of the remifentanil groups (3 and 0% in Group II and III, respectively) than in the control group (70%). Remifentanil in both of the remifentanil groups attenuated the increase in heart rate and MAP immediately after endotracheal intubation and 1 minute after intubation.

Conclusion. The pretreatment with remifentanil in both 0.5 and 1.0 µg/kg of bolus doses dramatically prevented the withdrawal movements caused by the rocuronium injection, and effectively blunted the cardiovascular activation following by laryngoscopy and endotracheal intubation.

Key words: remifentanil, rocuronium, injection pain, withdrawal movements
Remifentanil can prevent the withdrawal movements due to the intravenous injection of rocuronium

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I. Introduction

Rocuronium is a non-depolarizing muscle relaxant of intermediate duration of action. As it currently has the fastest onset of action among non-depolarizing muscle relaxants,¹ rocuronium is widely used as an attractive alternative to succinylcholine in cases which rapid control of the airway is needed.² However, rocuronium causes some degree of pain during intravenous injection.³⁴ Most patients complain of severe burning pain in their arms even with only a subparalyzing dose for the prevention of fasciculation or accelerating muscle relaxation for endotracheal intubation in awake patients.³ Even after loss of consciousness from induction, IV rocuronium can still elicit withdrawal movements such as withdrawal of the injected hand and arm or a generalized movement of the body.⁴⁵

Generally, injection pain of rocuronium is reported to occur in 50-80% of patients.³ And the withdrawal movements observed in anesthetized patients have been attributed to the pain from injection of rocuronium.⁴ These withdrawal movements
may cause dislocation or displacement of the IV catheter, causing difficulty in administrating additional drugs and subsequent risk of cardiovascular activation.\textsuperscript{6,7}

Thus, numerous methods have been suggested to attenuate these withdrawal movements related to rocuronium induced pain, but a dramatic, available and convenient way with a satisfactory low failure rate and without side effects has not still been found. From this point of view, the establishment of a more convenient way of preventing the injection pain by rocuronium is mandatory.

Remifentanil is a synthetic and esterase-metabolized opioid with a rapid onset, an ultra-short duration of action and a stable, short context-sensitive half-time compared with other opioids.\textsuperscript{8,9} Therefore, hemodynamic alterations by this drug, such as, decreases in blood pressure and heart rate, can be expected to last shorter than by alfentanil, sufentanil, or fentanyl. These characteristics have recently made remifentanil an ideal coping drug against noxious stimuli.

The purpose of this study was to determine whether remifentanil could prevent or attenuate the rocuronium-induced withdrawal movements when treated prior to rocuronium injection at a bolus dose used commonly in the clinical practice. In addition, the effects of pretreated remifentanil on cardiovascular responses following by laryngoscopy and endotracheal intubation were investigated.
II. Materials and methods

After obtaining both the approval from the institutional IRB and the written informed consents from the patients, 90 female patients undergoing elective thyroidectomy under general anesthesia and satisfying ASA physical status I or II with an age-range between 19 and 65 years were qualified as subjects. Patients with severe hypertension, diabetes, ischemic heart diseases, severe bradycardia, chronic pain syndrome, neuromuscular disorders, or Parkinsonism were excluded. Patients who had received analgesics or sedatives within the previous 24 hours were also ruled out from this study.

On the day of the operation, a 20 gauge intravenous cannula was inserted at the distal part of the forearm cephalic vein of each patient. The free flow of Ringer’s lactate solution or normal saline was confirmed by gravity. Thirty minutes prior to induction of anesthesia, 0.004 mg/kg of IV glycopyrrolate was given to each patient, but midazolam was not administered because it could affect pain sensation. Patients were monitored with noninvasive mean arterial pressure (NIBP), pulse oxymeter and electrocardiogram throughout their stay in the operating room. In addition, to evaluate the effect of remifentanil on the onset time of rocuronium, accelerography (TOF-Watch SX, Organon) electrodes were placed on the ulnar nerve area of the wrist.

Ninety recruited patients were randomly allocated to 3 Groups, then three different regimens were applied to the groups as is shown in Table 1.
Table 1. Protocol of administration of drugs

<table>
<thead>
<tr>
<th></th>
<th>Regimen prior to rocuronium injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>4 ml of N/S</td>
</tr>
<tr>
<td>Group II</td>
<td>4 ml of 0.5 µg/kg of remifentanil in N/S</td>
</tr>
<tr>
<td>Group III</td>
<td>4 ml of 1 µg/kg of remifentanil in N/S</td>
</tr>
</tbody>
</table>

N/S: normal saline

The administered doses of remifentanil for Group II and III were 0.5 µg/kg and 1.0 µg/kg, respectively. The administered volume of the remifentanil solution was adjusted to 4 ml by mixing normal saline before it was administered to the patients of Group II and III. To the patients of Group I (control), only 4 ml of saline was administered. The syringe containing the study drug was selected in a randomized manner by another anesthesiologist who was blinded to the study.

In each Group, 4 ml of normal saline and the same volume solution containing different doses of remifentanil was administered over 30 seconds. Thirty seconds after the administration of the study drug, anesthesia was induced with 5mg/kg of thiopental which was injected at the rate of 0.5 ml/sec. Immediately after the administration of thiopental, mask ventilation with 5 L/min flow O₂ was started. The accelerogram (TOF-Watch, Organon®, Netherland) was calibrated automatically to set up the control twitch height, and continuous 1Hz-single twitch monitoring was carried out. Twenty seconds after the administration of thiopental when the patient was unconscious and the eyelash reflex was abolished, rocuronium in the amount of 0.6 mg/kg was injected at the rate of 0.5 ml/sec. During the injection of rocuronium, the movements of hands, arms or shoulders were observed by another
anesthesiologist who was blinded to the regimen of the pretreated drug.

To estimate the incidence of the withdrawal response, a 4 point grading system was employed as shown in Table 2, in which the patient’s response to the injection of rocuronium was classified accordingly.

**Table 2. Grading of withdrawal response**

<table>
<thead>
<tr>
<th>Degree of movement</th>
<th>Patient’s response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No response or withdrawal</td>
</tr>
<tr>
<td>1</td>
<td>Movement at the wrist only</td>
</tr>
<tr>
<td>2</td>
<td>Movement/withdrawal involving arm only</td>
</tr>
<tr>
<td>3</td>
<td>Generalized response-withdrawal or movement in more than one extremity, cough, or breath-holding</td>
</tr>
</tbody>
</table>

Then, anesthesia was maintained with 3.0 vol % sevoflurane in 100% O₂ until the end of the study. The accelerogram was used to evaluate the effect of remifentanil on the onset time of rocuronium. In this study, the onset time of rocuronium was defined as the time gap from the end of 0.6 mg/kg of rocuronium injection to the maximal depression of the single twitch. The onset time of rocuronium in each Group was measured and compared. Twenty seconds after the single twitch value fell to zero, endotracheal intubation was performed. Mask ventilation and intubation was performed by the same anesthesiologist.

In this study, the mean arterial pressure (MAP) and heart rate before (baseline) and during induction (prior to intubation, immediate post-intubation, 1 min after intubation, 2 minutes after intubation, respectively) were measured, in order to clarify the effect of remifentanil on the cardiovascular response following by
laryngoscopy and endotracheal intubation. The side effects after remifentanil injection such as bradycardia (more than 20% decrease of baseline heart rate), chest tightness, muscle rigidity, desaturation (SpO₂ < 90%), and the frequency of cough development were also checked. Patients who showed coughing more than two times just after the injection were designated as cough positive (+) cases.

**Statistical Analysis**
Statistical analyses were performed using SPSS for Windows version 13.0 software (Chicago, IL). This study required at least 30 patients per Group for reliable analysis on the basis of power analysis.

With respect to the comparison of patient characteristics such as age, height, weight and the onset time of rocuronium, One-way ANOVA was used. For the comparison of non-parametric data of withdrawal responses between the three Groups, the Kruskal-wallis test was used. Regarding the comparison of the frequency of cough development between Groups II and III, the Fisher exact test was used. The results were considered statistically significant when the \( P \) value was less than 0.05.
III. Results

The groups did not differ significantly regarding age, weight, and height (see Table 3).

Table 3. Patients’ age, weight and height, and the onset time of rocuronium

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>42.8 ± 10.27</td>
<td>43.9 ± 11.15</td>
<td>42.8 ± 11.48</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.3 ± 8.08</td>
<td>57.7 ± 5.91</td>
<td>55.2 ± 6.82</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.6 ± 5.68</td>
<td>159.9 ± 6.05</td>
<td>158.2 ± 5.82</td>
</tr>
<tr>
<td>Onset Time (sec)</td>
<td>59.1 ± 16.55</td>
<td>61.3 ± 13.70</td>
<td>56.9 ± 10.49</td>
</tr>
</tbody>
</table>

All values are mean ± SD. Onset Time: the onset time of rocuronium.

Group II and Group III, in which 0.5 and 1 µg/kg of remifentanil was pretreated respectively, showed remarkably decreased withdrawal movements due to the rocuronium injection compared to control Group I. There was no significant difference in the degree of withdrawal movements between Group II and III (see Table 4).

Table 4. Withdrawal response scores in three groups

<table>
<thead>
<tr>
<th>Withdrawal response scores</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>9 (30)</td>
<td>12 (40)</td>
<td>4 (13)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Group II</td>
<td>29 (97)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Group III</td>
<td>30 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Data are number of patients (%). Group I (control Group) showed definitely higher withdrawal response scores than did Group II and III. Abrupt decreasing tendency of withdrawal response scores in Group II and III can be observed.

Groups II and III showed lower heart rates and MAPs compared to the control Group (Group I) during anesthetic induction (see Fig. 1 and Fig. 2). Remifentanil in both 0.5 and 1.0 µg/kg concentrations attenuated the increase in heart
rate and MAP especially immediately after endotracheal intubation and 1 minute after intubation. There existed no statistical difference in this cardiovascular blunting effect between Group II and III.

As for the heart rate, the blunting effect in Group II and III persisted until 1 min after intubation and was diminished by 2 min after intubation (see Fig. 1). No severe bradycardia was found in Group II and III. On the other hand, the remifentanil’s blunting effect on the MAP was definite in both Group II and III until 1 minute after intubation, but this effect persisted until 2 minutes after intubation only in Group III (see Fig. 2).

![Graph](image)

**Fig. 1.** Changes in heart rate during anesthetic induction. Group II and III showed statistically significant blunting effect on heart rate increase compared with control Group (Group 1) at immediately after intubation, and this blunting effect appeared to persist until 1 minute after intubation. Base: before induction, Pre-intu: just before endotracheal intubation, imm.postintu: immediately after endotracheal intubation, postintu.1min: 1 minute after endotracheal intubation, postintu 2min: 2 minutes after endotracheal intubation. *p=0.012, † P=0.985, **p=0.007 ‡ p=0.043, § p=0.945, §§ p=0.039.
Fig. 2. Changes in mean arterial pressure (MAP) during anesthetic induction. Group II and III showed significant blunting effect on MAP increase compared with control Group I at immediately after intubation and 1 minute after intubation time. Base: before induction, Pre-intu: just before endotracheal intubation, imm.postintu: immediately after endotracheal intubation, postintu.1min: 1 minute after endotracheal intubation, postintu 2min: 2 minutes after endotracheal intubation. *p=0.000, † P=0.987, **p=0.000, ‡ p=0.036, §p=0.617, §§ p=0.002, ♦ p=0.008.

Regarding the side effects after remifentanil injection, the only main side effect observed was coughing, although two cases of chest tightness, one in Group II and one in Group III, were observed. Groups II and III showed cough attacks in 3 and 8 cases, respectively. Group II, in which 0.5 µg/kg of remifentanil was used, showed a lesser frequency of cough attacks than did Group III, yielding a significant difference in the cough attack rate between the two groups (Group II vs. Group III).

The onset time of rocuronium was not affected by the dosages of remifentanil. The average onset times for Groups I, II and III were 59.1, 61.3 and 56.9 seconds, respectively (see Table 3).
IV. Discussion

In this study, we found that pretreatment with remifentanil in both 0.5 and 1.0 µg/kg of bolus doses dramatically prevented the withdrawal movements caused by the rocuronium injection, and effectively blunted the cardiovascular activation following by laryngoscopy and endotracheal intubation.

Since rocuronium can induce muscle relaxation within 1 minute when a bolus of large amount is used (more than 0.9mg/kg), it can be an attractive alternative to succinylcholine\(^2\). However, the withdrawal response due to the injection pain may make rocuronium the next choice to succinylcholine in rapid sequence intubation.\(^2\) Also, the withdrawal responses can be a problem in that they may cause dislocation or displacement of the IV catheter, leading to inadequate administration of additional drugs, subsequently leading to difficulties in airway management or cardiovascular activation.\(^7\)

Thus, numerous methods have been suggested to attenuate these withdrawal movements related to rocuronium induced pain; pretreatments using lidocaine,\(^{10}\) ondansetron,\(^{11,12}\) metoclopramide,\(^{13}\) sodium bicarbonate,\(^{14}\) magnesium sulphate,\(^{14}\) fentanyl,\(^{11}\) ketamine,\(^{15}\) or alfentanil\(^{14}\) prior to an injection of rocuronium or an injection of a mixture of rocuronium and sodium bicarbonate\(^{16,17}\) or a mixture of rocuronium and lidocaine.\(^{18}\) But these pretreatment methods are limitedly effective and not always convenient because they often require the use of the tourniquet. The
method using a mixture of rocuronium and lidocaine has not shown definite side effects, but was found to be minimally effective in reducing the injection pain of rocuronium. And, a mixture of rocuronium and sodium bicarbonate can form carbon dioxide bubbles.

In this study, even a bolus dose of 0.5 µg/kg of remifentanil prior to rocuronium injection nearly completely reduced the withdrawal response. Thus, it is concluded that even a half dose (0.5 µg/kg) of 1.0 µg/kg of remifentanil, which is commonly recommended bolus dose of remifentanil 1-2 minutes prior to intubation, is effective in preventing the withdrawal responses due to the injection pain of rocuronium. These results are very encouraging compared to other previous results in that the method is convenient and has a low failure rate.

Also, remifentanil was not only applied to reduce the withdrawal responses, but to attenuate the hemodynamic changes during endotracheal intubation in this study. Hemodynamic effects by remifentanil, such as decreases in blood pressure and heart rate, can be expected to last shorter than by alfentanil, sufentanil, or fentanyl. According to Hall et al, in induction of anesthesia with propofol, rocuronium and 1% isoflurane, a bolus dose of 0.5 µg/kg of remifentanil followed by an infusion rate of 0.25 µg/kg/min effectively blunted the sympathetic activation during endotracheal intubation. In the present study, the bolus injection of remifentanil was not followed by infusion, instead, 1.5 MAC of sevoflurane was combined. According to our data, a bolus dose of 0.5 µg/kg of remifentanil and 1.0 µg/kg of remifentanil showed
similarly effective results in attenuating the hemodynamic change during endotracheal intubation.

In this study, it was demonstrated that the onset time of rocuronium was not affected by the dosage of remifentanil. Though 3.0 vol% sevoflurane was used for anesthetic induction in this study, it is unlikely that the use of such a low concentration of sevoflurane has a significant effect on hastening an onset time of muscle relaxation.

Meanwhile, the marked side effects of remifentanil such as bradycardia, chest tightness, muscle rigidity and desaturation were not found in this study. The only important side effect observed was coughing. Groups II and III showed cough attacks (more than two times of coughing after injection of remifentanil) in 3 and 8 cases respectively. Group II, in which 0.5 \( \mu \text{g/kg} \) of remifentanil was used, showed a lesser frequency of cough attacks than did Group III. Based on our results, the reduction of the frequency of coughing upon the injection of remifentanil can be achieved by the selection of an optimal dosage of remifentanil.

In the present study, patients in the age range of 19-65 years were enrolled, therefore pediatric patients were excluded. In pediatric patients, a withdrawal incidence of 83% to 84% was observed after injection of rocuronium, and an incidence of generalized movement of 48-49% was reported, compared to only 14% in adult patients.\(^{20}\) Also, while only 13% male patients demonstrated withdrawal responses, 30% of the female patients demonstrated withdrawal movements.\(^{21}\)
Moreover, 22% of females had severe reactions compared to only 5% of males. Recruitment of only female subjects excluding pediatric subjects substantially contributed to get a homogenous cohort in this study, leaving a further investigation about whether the promising conclusion drawn from female subjects holds true either in pediatric cohort behind.

In selecting study subjects, we excluded the patients with extremely old and young ages, and severe bradycardia (<45bpm). In these patients, remifentanil may give rise to harmful effects such as abrupt bradycardia or hypotension. Based on the results of this study, a smaller dose of remifentanil, i.e. a dose of 0.5 µg/kg of remifentanil, may be recommended to elderly patients and patients with bradycardia, because a lower dosage also exhibits the similar effect in preventing the withdrawal responses and attenuating cardiovascular activation.

In conclusion, we demonstrate that pretreatment with remifentanil in both 0.5 and 1.0 µg/kg of bolus doses dramatically prevented the withdrawal movements caused by the rocuronium injection, and effectively attenuated the cardiovascular activation following by laryngoscopy and endotracheal intubation.
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국문요약

Remifentanil 전처치로 rocuronium 정주에 따른 회피반응을 예방할 수 있다

목적: 비교적 빠른 발현시간과 중등도의 효과지속 시간을 가지고 있는 rocuronium은 높은 빈도의 정주통과 이로 인한 회피반응을 유발시킨다. Remifentanil은 빠른 발현시간과 짧은 효과 지속시간을 갖는 μ-opioid 수용체 효과로써, 본 연구에서는 임상에서 흔히 사용되는 일회정주용량인 1 µg/kg 또는 저혈량 상태나 고령환자에게 사용될 수 있는 0.5 µg/kg의 remifentanil 일회정주가 rocuronium으로 인한 회피반응과 마취 유도 시 후두경술과 기관내삽관에 따르는 심혈관계반응에 미치는 영향을 알아보고자 하였다.

방법: 전신마취하에 갑상선 수술을 시행받는 90명의 성인 여성 대상을 대상으로 하였다. 무작위 맹검법에 의해 30명씩 균등하게 세 군으로 할당하여, Group I은 생리식염수 4 ml, Group II와 III은 각각 0.5와 1 µg/kg의 remifentanil을 생리식염수로 희석하여 4 ml로 만들어 전완부 두부정맥에 거치된 20G의 도관에 30초에 걸쳐 정주하였다. Remifentanil 정주 30초 후에 thiopental 5 mg/kg를 0.5 ml/sec의 속도로 정주하면서 마취를 유도하였으며, thiopental 정주 20초 후에 rocuronium 0.6mg/kg을 0.5 ml/sec의 속도로 정주하면서 환자의 회피반응의 유무와 정도를 측정하였다. 또한 기관내삽관 전과 후의 혈압과 심박수를 측정하였다.

결과: 회피반응의 빈도와 정도는 Group II, III에서 Group I에 비해 현저하게 낮았으며, 또한 Group II, III에서 Group I에 비해 후두경술과 기관내삽관에 따르는 혈압과 심박수의 증가가 약화되었다. 결론: Remifentanil 1 µg/kg뿐만 아니라, remifentanil 0.5 µg/kg의 전투여도 rocuronium 정주에 따른 회피반응을 현저하게 감소시켰으며, 마취유도 시 후두경술과 기관내삽관에 따르는 혈압과 심박수의 증가를 약화시켜 혈액학적 안정성을 유지시키는데 효과가 있었다.

Key words: remifentanil, rocuronium, injection pain, withdrawal movement,