Original article

Peri-intubation hemodynamic changes during low dose fentanyl, remifentanil and sufentanil combined with etomidate for anesthetic induction

ZHANG Guo-hua and SUN Li

Keywords: etomidate; response to endotracheal intubation; bispectral index; opioids

Background Although etomidate is associated with very few cardiovascular side-effects and minimal histamine release, it has a less inhibitory effect on the pharyngolaryngeal reflex. Hence, blunting the responses to endotracheal intubation is more dependent of opioids for etomidate-based anesthetic induction. This prospective, randomized, double-blinded study was designed to investigate the effects of low dose remifentanil, fentanyl or sufentanil on etomidate induction with respect to hemodynamics, conscious level changes and drug consumption.

Methods Ninety unpremedicated and normotensive patients with American Society of Anesthesiologists (ASA) physical status I or II undergoing elective major abdominal surgery were randomly assigned in a double blinded fashion to each of the three groups: groups F, R and S. A bolus dose of fentanyl 1 µg/kg, sufentanil 0.1 µg/kg or remifentanil 1 µg/kg was given over 60 seconds in groups F, S and R, respectively. In each instance this loading dose was followed by a continuous infusion (0.1, 0.01 or 0.1 µg·kg⁻¹·min⁻¹ of fentanyl, sufentanil or remifentanil, respectively). After 5 minutes from start of opioid infusion, etomidate was titrated at a rate of 20 mg/min to a decrease in bispectral index (BIS) to 50. The time from administration of etomidate to loss of eyelash reflex or to a decrease in BIS to 50 was recorded. The blood pressure and heart rate were also recorded at different five time points. The average maximum percent changes of systolic blood pressure ([maximal or minimal measuring value–baseline]/baseline×100%) were calculated.

Results The time and the dosage of etomidate necessary to loss consciousness were greater in group F ((70.0±15.6) seconds; (0.35±0.05) mg/kg) than in groups S ((52.3±15.9) seconds; (0.26±0.06) mg/kg) and R ((56.2±20.2) seconds; (0.27±0.07) mg/kg) (P <0.01). The three groups took similar time and amount of etomidate to achieve an adequate depth anesthesia (BIS=50). The average maximum changes of systolic blood pressure were significantly different among the three groups: F, (25±6)% vs R, (13±4)% or S, (12±5)% (P <0.001). The endotracheal intubation caused marked increases in blood pressure and heart rate in groups F and S, but not in group R, respectively (P <0.01). The great hemodynamic changes occurred more frequently in group F than in groups R and S (P <0.01). The incidence of heart rate decreases of more than 30% of the baselines after induction was higher in group R compared with groups F and S (P <0.01).

Conclusions In normotensive and unpremedicated young adult patients receiving etomidate induction, low dose remifentanil or sufentanil significantly reduced the time and the amount of etomidate taken to loss unconsciousness compared with low dose fentanyl, but similar time interval and doses of etomidate were required to acquire adequate depth of anesthesia (BIS=50) for these three opioids. Remifentanil was more effective in blunting the cardiovascular responses to endotracheal intubation, nevertheless, accompanying significant lower heart rate after induction.

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etomidate is a popular used anesthetic induction agent in the clinical practice, which is characterized by rapid onset, very few side effects on cardiovascular and respiratory functions, as well as minimum histamine release. However, it has less inhibitory effect on pharyngolaryngeal reflex. Consequently, opioids is often combined with etomidate for anesthetic induction. Since the pharmacodynamic profiles of opioids are different from each other, it is important to determine which kind of opioids is more favorable to be used with etomidate to produce a smooth anesthetic induction and minimize the adverse effects. Fentanyl, remifentanil, and sufentanil are all commonly used opioids in the clinical practice. But most of studies concerning these three opioids used for anesthetic induction were often performed under the propofol-based induction and there were big differences in drug doses and measuring variables. The bispectral index (BIS) has been proposed as a measure of hypnotic state and so of the depth of anesthesia. Lallemand et al had proved a BIS value of 50 to be a reliable indicator of adequate depth of anesthesia for etomidate induction. Moreover, BIS-titrated anesthesia allowed less consumption of anesthetic agents with advantage of preventing

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intraoperative awareness and explicit recall. Therefore, in this study a BIS monitor was used during anesthetic induction with etomidate and small doses of remifentanil, fentanyl or sufentanil. We aimed to investigate the effects of these three opioids on etomidate consumption, peri-intubation hemodynamics and conscious level changes.

**METHODS**

**Subjects**

After institutional ethical approval and informed consent were obtained, 90 adult patients with American Society of Anesthesiologists (ASA) physical status I or II undergoing elective major abdominal surgery under general anesthesia were enrolled in the study. The characteristics of the patients were shown in Table 1. Exclusion criteria include: the patients with neurological, respiratory or cardiovascular diseases, hepatic and renal dysfunction, those who have taken drugs known to affect neurological or cardiovascular function and those with predicted difficult airway or aged over 60 years.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group F (n=30)</th>
<th>Group R (n=30)</th>
<th>Group S (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44±12</td>
<td>45±15</td>
<td>43±13</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>16/14</td>
<td>20/10</td>
<td>13/17</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.9±9</td>
<td>69±10</td>
<td>67.8±8</td>
</tr>
<tr>
<td>ASA status (I/II)</td>
<td>23/7</td>
<td>22/8</td>
<td>23/7</td>
</tr>
<tr>
<td>Intubation time (seconds)</td>
<td>27.5±10.2</td>
<td>23.3±9.3</td>
<td>26.2±11.4</td>
</tr>
</tbody>
</table>

Table 1. The physical characteristics in the patients

Intubation time defined as the time from insertion of a laryngoscope to placement of an endotracheal tube into the trachea. There were no significant differences with respect to physical characteristics and intubation time among the three groups.

All subjects were randomly allocated in a double-blind fashion using a sealed envelope technique into three groups (n=30 in each group), groups F, R and S. In groups F, S and R, the patients were given a bolus dose of fentanyl 1 µg/kg, sufentanil 0.1 µg/kg or remifentanil 1 µg/kg over 60 seconds, followed by a continuous infusion of 0.1 µg·kg⁻¹·min⁻¹, 0.01 µg·kg⁻¹·min⁻¹ or 0.1 µg·kg⁻¹·min⁻¹ (Graseby 3500 Diprifusor®; Graseby Medical Ltd, Watford, UK), respectively. The solutions containing opioids were prepared and administrated by an anesthesiologist who was not involved in data recording.

**Anesthetic induction**

All patients were unpremedicated and fasted overnight. On arrival at the operating room, the monitoring of electrocardiogram, noninvasive blood pressure, pulse oximetry, end-tidal carbon dioxide and BIS (Aspect Medical Systems Inc., Natick, MA, USA) were applied. After all patients were prehydrated with 7 ml/kg lactated Ringers solution, the baseline values of heart rate (HR), systolic and diastolic blood pressure (SBP and DBP), pulse oxygen saturation (SPO₂) were recorded. The patients were preoxygenated via a face mask for 5 minutes and anesthetic induction was initiated with fentanyl, remifentanil and sufentanil in groups F, R, S, respectively, according to the opioids administration regimens described above. After 5 minutes from start of opioid infusion, etomidate was titrated at a rate of 20 mg/min to a decrease in BIS to 50. Then, rocuronium 0.6 mg/kg was given to facilitate endotracheal intubation which was performed one minute after injection of the muscle relaxant using a Murphy endotracheal tube of internal diameter (ID) 7.5 mm or 7.0 mm in male and female patients, respectively. The patients’ lungs were ventilated to keep end-tidal carbon dioxide concentration within normal range and sevoflurane 2% (dailed concentration) was delivered in 100% oxygen at a fresh gas flow of 2.5 L/min.

**Measuring variables**

The intubation time from insertion of a laryngoscope to placement of an endotracheal tube into the trachea was recorded. Two kinds of induction time, from administration of etomidate to loss of eyelash reflex and to a decrease in BIS to 50 were also recorded. The consumptions of etomidate at t1 and t2 time points were calculated. SBP, DBP and HR were recorded immediately before intubation (T0), at intubation (T1), and 1 minute (T2), 3 minutes (T3) and 5 minutes (T4) after intubation. The maximum percent change of SBP (maximal or minimal measuring value–baseline/baseline×100%) for each patient and the average value of that for each group during observation period were calculated. The numbers of patients who experienced great hemodynamic changes were noted: SBP or HR increases or decreases of more than 30% of baselines, SBP<90 mmHg or >140 mmHg; HR<50 beats per minute or >100 beats per minute. The patients who required more than one attempt or 60 seconds to achieve successful endotracheal intubation were excluded from analysis.

**Statistical analysis**

Statistical analyses were performed using SPSS 11.0 (SPSS, Chicago, IL, USA). The continuous and discrete variables were expressed with mean±standard deviation (SD) or the numbers of patients, respectively. The hemodynamic data were analyzed with two-way analysis of variance (ANVOA) with post hoc Bonferroni test. The other continuous data were compared with one-way ANVOA or Kruskal-Wallis test for non-normal distribution. Discrete data were analyzed with chi-square test or Kruskal-Wallis test as appropriate. P <0.05 was considered statistically significant.

**RESULTS**

All patients were successfully intubated as required by the study protocol. The patients’ physical characteristics and the intubation time were comparable among the three groups (Table 1). The time and the dosage per body weight of etomidate necessary to loss consciousness were greater in group F than in groups S and R (F vs S or R for both time and dosages, P <0.01), but those two variables for achieving an adequate anesthesia (BIS=50) were not significantly different among the groups (Figures 1 and 2).
After intubation (minutes)

### Table 2. Hemodynamic changes associated with anesthetic induction and intubation (mean±SD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baselines</th>
<th>T0</th>
<th>T1</th>
<th>1 (T2)</th>
<th>3 (T3)</th>
<th>5 (T4)</th>
<th>Max SBP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group F</td>
<td>124±10</td>
<td>120±12</td>
<td>153±13 $^*$</td>
<td>142±11 $^*$</td>
<td>129±10</td>
<td>122±11</td>
<td>25±6</td>
</tr>
<tr>
<td>Group R</td>
<td>125±9</td>
<td>109±9 $^*$†</td>
<td>122±11 †‡</td>
<td>118±12 $^*$†‡</td>
<td>112±13 $^*$†‡</td>
<td>110±12 $^*$†</td>
<td>13±4 †</td>
</tr>
<tr>
<td>Group S</td>
<td>125±10</td>
<td>116±11 $^*$</td>
<td>137±14 $^*$</td>
<td>130±12 $^*$</td>
<td>123±13</td>
<td>117±11 $^*$</td>
<td>12±5 †</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group F</td>
<td>74±12</td>
<td>70±12</td>
<td>89±13 $^*$</td>
<td>82±10 $^*$</td>
<td>77±9</td>
<td>70±8</td>
<td>–</td>
</tr>
<tr>
<td>Group R</td>
<td>71±13</td>
<td>59±9 $^*$†</td>
<td>69±11 $^*$†</td>
<td>66±10 $^*$</td>
<td>64±8 $^*$</td>
<td>64±9 $^*$</td>
<td>–</td>
</tr>
<tr>
<td>Group S</td>
<td>70±11</td>
<td>66±9</td>
<td>78±11 $^*$†</td>
<td>72±10 $^*$</td>
<td>68±9 $^*$</td>
<td>67±8 $^*$</td>
<td>–</td>
</tr>
<tr>
<td><strong>HR (beats per minute)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group F</td>
<td>76±8</td>
<td>74±9</td>
<td>97±10 $^*$</td>
<td>94±8 $^*$</td>
<td>88±11 $^*$</td>
<td>85±10 $^*$</td>
<td>–</td>
</tr>
<tr>
<td>Group R</td>
<td>77±9</td>
<td>61±8 $^*$†</td>
<td>82±10 $^*$†</td>
<td>80±8 $^*$</td>
<td>74±11 $^*$</td>
<td>74±9 $^*$†</td>
<td>–</td>
</tr>
<tr>
<td>Group S</td>
<td>78±10</td>
<td>71±8</td>
<td>90±9 $^*$†</td>
<td>84±10 $^*$</td>
<td>85±12 $^*$</td>
<td>80±11 $^*$</td>
<td>–</td>
</tr>
</tbody>
</table>

$n=30$ for each group. $^*$P < 0.05 compared with the baselines. $^†$P < 0.05 compared with group F. $^‡$P < 0.05 compared with group S. SBP: systolic blood pressure. DBP: diastolic blood pressure. HR: heart rate. Max SBP: the average maximum percent changes of SBP during the observation period. T0=after anesthetic induction. T1=at intubation. T2, T3, T4=1, 3, 5 minutes after intubation, respectively.

**DISCUSSION**

Our results showed that during BIS-guided etomidate...
Table 3. The numbers of patients experienced great hemodynamic changes

<table>
<thead>
<tr>
<th>Groups</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Heart rate (beats per minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥30% ≥30% ≥30% ≥30% ≥30% ≥30%</td>
<td>≥30% ≥30% ≥30% ≥30% ≥30% ≥30%</td>
</tr>
<tr>
<td>F</td>
<td>14  25  0  16  0  12  0</td>
<td>0  0  0  0  0  0  0</td>
</tr>
<tr>
<td>S</td>
<td>0  0  14  0  0  0  0</td>
<td>2  0  0  6  0  0  2</td>
</tr>
<tr>
<td>R</td>
<td>0  0  0  0  0  0  0</td>
<td>0  0  0  0  0  0  0</td>
</tr>
</tbody>
</table>

Values are the numbers of the patients. *P <0.01, compared with group F. †P <0.01, compared with group S. *Percent increases or decreases of SBP or HR are ≥30% or <30% of the baselines, respectively.

The doses of the opioids used in the present study were determined on the basis of previous studies comparing the profiles of anesthetic induction with these three kinds of opioids.8-12 Since the relative potencies of sufentanil, remifentanil and fentanyl are 10:1:1, both the bolus and infusion doses for these three opioids in our study can be considered as equal potency. As a matter of fact, because the context-sensitive half-time of remifentanil is so short as to result in a rapid declination in the plasma concentration of it, especially after a single bolus, it seems to be difficult to establish an equipotent comparison of these opioids. The administration regimen using a single bolus injection plus continuous infusion in our study aimed to maintain a stable drug plasma concentration as possible, which was in accordance with those of the other comparative studies.8,10

The BIS has been proposed as a measure of hypnotic state and so of the depth of anesthesia, although with confounding results.2,13 Lallemand et al2 found that for etomidate induction, a BIS of 50 was associated with the absence of purposeful movement during tracheal intubation and the absence of postoperative explicit recall. Iannuzzi et al10 also used a BIS <50 as an indicator of satisfactory depth of anesthesia in a study of comparing the effects of remifentanil and sufentanil on blunting the cardiovascular responses to tracheal intubation. However, BIS may not reflect the synergistic hypnotic effects of the opioids and intravenous anesthetics,3,16 which was demonstrated in our study by the fact that the three groups took different time to loss consciousness but similar time to achieve a BIS decrease in 50. This might because opioids actions on the “noncortical” regions for example, locus coeruleus, cannot be detected by BIS.14 Also, BIS value often shows a steep decrease during induction period, which tends to make the reading BIS value higher than the actual one. In addition, etomidate-induced myoclonia is likely to influence the BIS readings. We did not observe the myoclonia during the study period probably due to the use of opioids and the administration of etomidate with a infusion rather than a bolus.3-5,17

Cafiero’s study suggested that blood pressure and HR increases during intubation were better controlled with 0.2 µg·kg⁻¹·min⁻¹ infusion of remifentanil in comparison with 2 µg/kg bolus of fentanyl.11 The results of Wilhelm’s study comparing remifentanil (given as infusion at 0.5 µg·kg⁻¹·min⁻¹) and fentanyl (1.5 µg/kg bolus)-etomidate anesthetic induction showed that less doses of etomidate and more suppression on the cardiovascular response to intubation but also a 14% decrease in mean blood pressure were associated with remifentanil.1 Furthermore, in our study remifentanil or sufentanil had a greater suppression on the hemodynamic responses to intubation compared with fentanyl, which was consistent with ours. Furthermore, in our study remifentanil conferred more stable hemodynamics during intubation than sufentanil but was associated with a great decrease of HR after induction. However, in Iannuzzi and Casati’s studies,8,10 small doses of sufentanil and remifentanil, which were given in a similar administration regimen to ours, produced the comparable effects on blunting the cardiovascular response to intubation without significant changes in HR. This can be attributed to the differences in the intravenous induction agents and premedication. Our patients were unpremedicated and received etomidate for induction whereas the patients in Iannuzzi and Casati’s studies received atropine or midazolam as premedication and propofol for induction. Etomidate has less effects on inhibiting the upper airway reflex and producing vasodilatation than propofol6,7,18,19 and hence the use of propofol is likely to enhance the opioid effects, blurring the comparison between sufentanil and remifentanil, and also may account for the greater decrease in blood pressure associated with remifentanil-propofol induction compared with remifentanil-etomidate induction.1 In addition, small doses of fentanyl in the present study failed to suppress intubation response in view of about 50% patients on fentanyl experiencing the SBP or HR increase of more than 30% of the baseline. This is not surprising because that 500 µg of fentanyl has been proved to be necessary to abolish such an adverse response during etomidate induction.5

The disadvantage of using remifentanil is related to the great decreases in blood pressure and HR. Remifentanil-induced vasodilatation may be a contributing factor.20,21 In the remifentanil group of our
study, although the patients were prehydrated with 7 ml/kg lactated Ringers solution before induction, the percent decrease of SBP relative to the baseline still reached 12% and two patients experienced the episode of SBP<90 mmHg after induction. As well, 20% of patients receiving remifentanil had the HR decrease of more than 30% of the baseline with HR<50 beats per minute in two. These transient great hemodynamic changes will not cause adverse effects in healthy young adult patients, but seem to be a potential danger for cardiovascular compromised patients.

Notwithstanding our results, it is noteworthy that the endotracheal intubation was not performed at the time to peak effects of remifentanil, fentanyl and sufentanil in the present study. However, the administration regimen using a bolus followed by a continuous infusion is helpful to maintain a stable drug concentration, thereby may minimize this limitation of our study.8,10

In conclusion, in normotensive and unpremedicated young adult patients receiving etomidate induction, small doses of remifentanil or sufentanil significantly reduced the time and the amount of etomidate taken to loss consciousness compared with small dose of fentanyl, but similar time interval and doses of etomidate were required to acquire adequate depth of anesthesia (BIS=50) for these three opioids. Remifentanil was more effective in blunting the cardiovascular responses to endotracheal intubation, nevertheless, accompanying significant lower heart rate after induction.

REFERENCES


(Received February 28, 2009)