Different small-dose sufentanil blunting cardiovascular responses to laryngoscopy and intubation in children: a randomized, double-blind comparison†

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Background. Sufentanil is a potent opioid analgesic frequently used in clinical anaesthesia. This prospective, randomized, double-blind study was designed to assess the efficacy of different small-dose sufentanil attenuating the cardiovascular intubation response in healthy children, aiming at determining the optimal dose of sufentanil for this purpose.

Methods. A total of 165 children aged 3–9 yr were randomized to one of four groups to receive the following in a double-blind manner: normal saline (Group 1), sufentanil 0.1 μg kg⁻¹ (Group 2), sufentanil 0.2 μg kg⁻¹ (Group 3), and sufentanil 0.3 μg kg⁻¹ (Group 4). Anaesthesia was induced with propofol 2.5 mg kg⁻¹ and vecuronium 0.1 mg kg⁻¹. Non-invasive blood pressure (BP) and heart rate (HR) were recorded before induction of anaesthesia (baseline value), at immediately before intubation (post-induction values), at intubation, and at 1 min intervals for 5 min after intubation. The per cent changes of systolic blood pressure (SBP) and HR during the observation were calculated.

Results. Except for Group 4, tracheal intubation caused significant increases in BP and HR in Groups 1, 2, and 3 compared with baseline values. BP and HR at intubation and their maximum values during the observation were significantly different among the four groups. The maximum per cent increases of SBP and HR during the observation were 20 and 28% of baseline values, respectively, in Group 2, 13 and 13% in Group 3, and 0 and 4% in Group 4 compared with 24 and 37% in Group 1. Except for the Group 3 vs Group 4 comparison, the incidences of SBP and HR per cent increases >30% of baseline values were also significantly different among the four groups.

Conclusions. In combination with propofol for induction of anaesthesia in children, the bolus administration of sufentanil can produce a dose-related attenuation of the cardiovascular intubation response and sufentanil 0.3 μg kg⁻¹ can completely abolish the cardiovascular intubation response.

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Laryngoscopy and tracheal intubation in children can cause temporary significant cardiovascular response.¹ It could be potentially harmful, and avoidance of such circulatory changes during tracheal intubation may be crucial, for example in the presence of pulmonary hypertension, cerebrovascular malformation, or increased intracranial pressure.² It has been shown that small-dose fentanyl,³ remifentanil,⁴ and alfentanil⁵ can effectively attenuate the

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cardiovascular intubation response in children. Sufentanil is an analogue of fentanyl and has been used for induction and maintenance of anaesthesia in children.\(^6\)\(^7\) It is 5 to 10 times more potent than fentanyl and is a most potent opioid analgesic frequently used in clinical practice.\(^8\) Previous studies have demonstrated that in combination with propofol, a relatively small dose of sufentanil is effective in preventing the untoward cardiovascular intubation response in adults.\(^9\)\(^10\) In view of significant differences in sufentanil pharmacokinetics between adults and children,\(^11\) we hypothesized that the effective dose of sufentanil required to control the cardiovascular intubation response in children might differ from that in adults. However, there has been no evaluation of the optimal dose of sufentanil for attenuation of the cardiovascular intubation response in children. Therefore, this randomized, double-blind study was designed to assess the ability of different small-dose sufentanil to attenuate the cardiovascular intubation responses in healthy children, with the aim of determining the optimal dose of sufentanil for this purpose.

**Methods**

After institutional ethics committee approval and written informed consent from the parents were obtained, 165 children, ASA physical status I, aged 3–9 yr, undergoing elective plastic surgery under general anaesthesia requiring tracheal intubation were included in this study. Exclusion criteria were a history of reactive airway disease, gastroesophageal reflux, morbid obesity, a known allergy to any of the study drugs, a known or predicted difficult airway, hypertension, and use of medications and nutraceuticals known to affect blood pressure (BP) and heart rate (HR). Using a sealed envelope method, children were randomized to one of four study groups; each of 40 children to receive the following treatments in a double-blind manner: normal saline (NS) (Group 1), sufentanil 0.1 \(\mu g \cdot kg^{-1}\) (Group 2), sufentanil 0.2 \(\mu g \cdot kg^{-1}\) (Group 3), and sufentanil 0.3 \(\mu g \cdot kg^{-1}\) (Group 4). Each treatment was made up to 5 ml with NS. All treatments were prepared by an independent anaesthetist, and the investigators were blinded to the identity of the drugs.

Before surgery, all the children fasted overnight and were restricted from oral intake of clear fluid for 2–3 h. One hour prior to the child arriving in the operating room, EMLA\(^\text{®}\) cream (AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA) was applied to the dorsum of a hand as surface anaesthesia to facilitate placement of the i.v. catheter. After the child entered the operating room, non-invasive BP, HR, ECG (CM\(_3\) lead), and pulse oxygen saturation (\(S\text{PO}_2\)) were measured with a multifunction monitor (F-CUS, GE Healthcare, Helsinki, Finland). The width of blood pressure cuff used for a child was about two-thirds of the length of his or her upper arm. After a stabilization period of 5 min, baseline values of systolic blood pressure (SBP), diastolic blood pressure, mean arterial pressure, and HR were obtained from the average of the three measurements obtained 2 min apart. Then a 22-gauge i.v. catheter was inserted into the veins on the dorsum of a hand. Immediately before induction of anaesthesia, the multifunction monitor for measurement of BP was set to the continuous mode with a response time of \(~20–30\) s.

After routine pre-oxygenation, the study treatments were infused over a 30 s period using a motor-driven syringe pump, according to the random allocation. The anaesthetist who had prepared the treatments and was not involved in data recording activated the pump infusing the study drugs. After 2 min, anaesthesia was induced with propofol 2.5 mg \(kg^{-1}\) administered i.v. over a 30 s period. When the eyelash reflex was absent, the child was ventilated via a facemask with oxygen 100%. After confirmation of facemask ventilation, vecuronium 0.1 mg \(kg^{-1}\) was administered i.v. for muscle relaxation. If any difficulty was encountered in performing facemask ventilation, the child was excluded from the study and her/his card was resealed in an envelope and randomly placed among the remaining envelopes to be used later.

Tracheal intubation was started 3 min after propofol injection. All tracheal intubations were performed using a Macintosh laryngoscope (Timesco, London, UK) by the experienced anaesthetists in clinical anaesthesia and direct laryngoscopic tracheal intubations (>5 yr experience). The tracheal tube was inserted into the glottis until the cuff was 1 cm below the vocal cords under direct vision. Children who required more than one attempt to achieve successful intubation were excluded from the study. After intubation, the lungs were mechanically ventilated using a 60% nitrous oxide in oxygen mixture with a 1% inspired isoflurane at a fresh gas flow of 2.5 litre min\(^{-1}\). The ventilator settings were adjusted to maintain end-expired carbon dioxide level of 35–40 mm Hg. Inspired and end-expired concentrations of isoflurane, oxygen, nitrous oxide, and carbon dioxide were measured and displayed digitally.

An independent investigator, unaware of the child’s group assignment, observed and recorded the cardiovascular variables. BP and HR were recorded immediately before intubation (post-induction values), at intubation, and every minute for the first 5 min after intubation. The maximum and minimum values of BP and HR during the observed period were obtained from the recorded trace of the multifunction monitor. During the observation, a third person acted as the time keeper using a digital stopwatch, and the clock was started (0 s) when the facemask was removed from the child. The time keeper recorded three further times using the ‘lap’ function on the stopwatch: when ventilation was restarted through the tracheal tube and carbon dioxide was detected by capnography (intubation time), when maximum values of SBP and HR occurred (times required to reach maximum values of SBP and HR), and when SBP and HR recovered to within 10% of post-induction values. If SBP and HR did not recover to

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within 10% of post-induction values by 5 min after intuba-
tion, BP and HR were observed continuously until the
target values were achieved. The watch was stopped when
SBP and HR recovered to post-induction values. The times
from completion of intubation to recover the post-
induction values of SBP and HR (times required for recov-
ery of SBP and HR to post-induction values) were calcu-
dated. During the observation, no manipulation, including
movement of head and tube fixation, nor skin preparation
of operating field was performed.

The incidences of SBP and HR per cent changes >30%
of baseline values during the observation were recorded.
According to Chinese Practice Guideline of Clinical
Anesthesia,12 when anaesthesia is induced with combi-
nations of propofol and opioids in children aged 3–12 yr,
an acceptable lowest limit of HR is 65 beats min⁻¹ to
avoid severe cardiovascular depression. In this study,
therefore, a HR of <65 beats min⁻¹ was defined as brady-
cardia. If bradycardia occurred, atropine 5–10 \( \mu \) g kg⁻¹
was injected i.v. to treat, and patient was excluded from
statistical analysis of the data. Also, arrhythmia, if present
and lasted for >10 s, was noted. An arrhythmia was
defined as any ventricular or supraventricular premature
beat or any rhythm other than sinus.

The statistical analysis of data was performed with
SPSS (version 11.5, SPSS Inc., Chicago, IL, USA) and a
POMS (version 5.0, Shanghai Scientific and Technical
Publishers, Shanghai, China) statistical software.
Non-parametric data from the four groups were compared
using the 2 × 4 contingency test. Parametric data from the
data per cent increases ofSBP and HA were significantly
different among the four groups. Times required for recov-
ery of SBP and HR to post-induction values were signifi-
cantly different among the four groups. The four groups
were similar with respect to the incidences ofSBP and HR
per cent decreases >30% of baseline values (Fig. 3).

There were no significant differences in times required
to reach maximum values ofSBP and HR among the four
groups. Times required for recovery of SBP and HR to
post-induction values were significantly different among
the four groups, except for the comparison between
Groups 3 and 4 (Table 2). Changes in cardiac rhythm
(premature atrial contraction and junctional rhythms)
associated with laryngoscopy and intubation were
observed in six children in Group 1, in four children in
Group 2, in two children in Group 3, and one child in
Group 4. All ectopic beats resolved spontaneously within
2 min without specific therapeutic intervention. No child
required treatment for bradycardia.

**Discussion**

This randomized, double-blind investigation was designed
to assess the ability of different small-dose sufentanil in
combination with propofol to attenuate the cardiovascular
intubation response in children, with the aim of determin-
ing the optimal dose of sufentanil for this purpose. This
would be useful for any patient who requires to avoid the

**Table 1** Patient characteristics. Values were expressed as mean(SD) except for
gender data, \( n = 40 \) each group. There were no statistically significant
differences in all characteristics of patients among the four groups

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<tr>
<td>Gender (mf)</td>
<td>27/13</td>
<td>25/15</td>
<td>26/14</td>
<td>26/14</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>6.7(1.5)</td>
<td>6.3(1.7)</td>
<td>6.2(1.4)</td>
<td>6.5(1.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>25(4)</td>
<td>24(5)</td>
<td>24(5)</td>
<td>26(6)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>117(10)</td>
<td>115(8)</td>
<td>116(9)</td>
<td>116(8)</td>
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hyperdynamic cardiovascular changes during laryngoscopy and tracheal intubation or when a prolonged opioid effect is desirable after intubation (e.g. cardiac surgery and craniotomy). A previous study has showed that the bolus use of sufentanil 0.2 μg kg⁻¹ can significantly attenuate, but not completely abolish, the cardiovascular intubation response in children. Therefore, a highest dose of 0.3 μg kg⁻¹ was used in this study.

In designing this study, we wanted to deliver the drugs propofol and sufentanil for induction of anaesthesia in such a way that their peak site effects occurred at the same time and hence most effectively attenuated the cardiovascular intubation response. In children aged 3–11 yr, Muñoz and colleagues found that after a bolus injection of propofol over <5 s, the times required to reach peak effect site concentration (t_peak) for propofol was 132 s. But an injection time of <5 s in this study may have resulted in a rapid effect site concentration and a short t_peak, because it depends on the speed of injection after a bolus. The t_peak of sufentanil has been shown to be 5–
Sufentanil and cardiovascular intubation response in children

Fig 3 The incidences of SBP and HR per cent changes >30% of baseline values during the observation in the four groups. Children in Groups 1, 2, 3, and 4 received normal saline, sufentanil 0.1 µg kg⁻¹, sufentanil 0.2 µg kg⁻¹, and sufentanil 0.3 µg kg⁻¹, respectively. Note: the incidences of SBP and HR per cent increases >30% of baseline values during the observation in Group 4 were 0%. *P < 0.05 compared with Group 1; †P < 0.05 compared with Group 2.

6 min in adults.¹⁸ There is no available information regarding the tpeak of sufentanil in children. It is clear, however, that onset of clinical effect is slower for sufentanil than for propofol.⁸⁻¹¹ According to our routine practice¹² ¹³ and the previous data,¹⁵ ¹⁷ therefore, sufentanil and propofol in this study were started 5 and 3 min before tracheal intubation, respectively. Both drugs were also administered i.v. >30 s to decrease the occurrence of severe cardiovascular depression after induction of anaesthesia in children.¹³ To exclude a bias, premedication was avoided in our children.¹⁸ Vecuronium was chosen for neuromuscular block as it is free from cardiovascular effects.¹⁹

The results of this study clearly showed that sufentanil results in a dose-related attenuation of the cardiovascular response to laryngoscopy and intubation in children. Our findings correspond with the results of previous studies involving low, medium, or high doses of sufentanil (up to 20 µg kg⁻¹) focused on its use as a supplement to balanced anaesthesia or as a sole anaesthetic in cardiac surgery in infants and children.⁶⁻⁷

Both SBP and HR at intubation exceeded baseline values in Group 2, and incidence of HR per cent increases >30% of baseline values reached up to 53%. In Group 3, SBP and HR at intubation increased above baseline values, but their maximal increases did not exceed 20% of baseline values. In Group 4, SBP and HR at intubation and their maximum values during the observation were not different from baseline values. In addition, incidences of SBP and HR per cent increases >30% of baseline values were higher in Group 2 than in Groups 3 and 4. These results indicate that the bolus use of sufentanil 0.1 µg kg⁻¹ is ineffective in controlling the cardiovascular intubation response whereas sufentanil 0.2 µg kg⁻¹ significantly decrease the cardiovascular intubation response to a clinically acceptable level and sufentanil 0.3 µg kg⁻¹ completely abolish the cardiovascular intubation response.

In two comparable studies in adults,⁹ ¹⁰ when anaesthesia was induced with propofol, the dose of sufentanil required to attenuate satisfactorily the cardiovascular intubation response was 0.1–0.14 µg kg⁻¹, which was significantly lower than that used in our children. This discrepancy can be explained by the pharmacokinetic differences between children and adults. It was found that the volume of distribution at steady state of sufentanil in children aged 2–8 yr was 1.5 times greater than that in adults when expressed as a function of body weight.¹¹ This means that a higher dose of sufentanil based on body weight (in µg kg⁻¹) is required to achieve similar effect in children compared with adults. These findings support our initial hypothesis that the effective dose of sufentanil required to control the cardiovascular intubation response may be different between children and adults. This also agrees with the results of previous studies on the clinical pharmacodynamics of remifentanil in which children require a remifentanil infusion rate almost two-fold higher than adults to block the somatic response to skin incision during propofol total i.v. anaesthesia or sevoflurane anaesthesia.²⁰ ²¹

In contrast, Moore and colleagues⁶ demonstrated that in children between 4 and 12 yr of age undergoing open heart surgery, the use of sufentanil as a sole anaesthetic in bolus form (5–20 µg kg⁻¹) did not provide a reliable attenuation of the cardiovascular intubation response. As a practical conclusion, we again emphasize the advantages associated with combination of a hypnotic and an opioid instead of a hypnotic or an opioid alone when treating noxious stimulation.⁸ ¹³

Unlike many other opioids, sufentanil alone produces much less cardiovascular instability. It may cause a reduction in HR and BP shortly after induction of anaesthesia, but the cardiovascular instability usually associated with surgery is largely avoided.⁵ The cardiovascular

Table 2 Times required to reach maximum values of SBP and HR (Times to MAXSBP or MAXHR), and times required for recovery of SBP and HR to the post-induction values after intubation (Recovery timesSBP or MAXHR) in the four groups. The times from removal of face mask to reach maximum values of SBP and HR during observation; the times from completion of intubation to recover post-induction values of SBP and HR. Values were expressed as mean±SD, n=40 each group. *P < 0.05 compared with Group 1; †P < 0.05 compared with Group 2.

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<tr>
<td>Times to MAXSBP(s)</td>
<td>130(57)*</td>
<td>106(37)*</td>
<td>75(28)#</td>
<td>69(32)#</td>
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<tr>
<td>Times to MAXHR(s)</td>
<td>128(69)</td>
<td>102(38)*</td>
<td>73(22)#</td>
<td>70(26)#</td>
</tr>
<tr>
<td>Recovery timeSBP(s)</td>
<td>130(57)*</td>
<td>106(37)*</td>
<td>75(28)#</td>
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response to sufentanil is likely secondary to opioid receptor-mediated central nervous system effects.22 In the present study, a fluid preload was not administered to children before induction of anaesthesia according to our routine practice. All children were undergoing elective surgery and were ASA I group patients. Our results showed that BP and HR in the three treatment groups significantly decreased from baseline values after induction of anaesthesia and at the end of the study period. These findings are in agreement with the results of other studies, which investigated the combinations of fentanyl, remifentanil, and alfentanil with propofol for induction of anaesthesia in children.3–5 13 17 24 The decreases in BP and HR after opiate agent and propofol are because of the synergistic action of the two drugs.8 17 It has been shown that opiate agents increase vagal tone and decrease sympathetic nervous activity.8 23 Except for sympathetic inhibition,25 propofol may also depress baroreceptor reflex control of HR.26

The most frequently reported disturbing side-effects after medium or high dose i.v. sufentanil administration are hypotension, chest wall rigidity, and bradycardia, which occurred at incidences of 6, 2.9, and 3.4%, respectively, in a large multicenter trial.8 We considered that the cardiovascular depression after a combination of small-dose sufentanil and propofol was not a problem in this study, since only a small proportion of children (3–8%) in cardiovascular depression after a combination of small-dose sufentanil and propofol may also depress baroreceptor reflex control of HR.26

The decreases in BP and HR after opiate agent and propofol are because of the synergistic action of the two drugs.8 17 It has been shown that opiate agents increase vagal tone and decrease sympathetic nervous activity.8 23 Except for sympathetic inhibition,25 propofol may also depress baroreceptor reflex control of HR.26

In summary, we demonstrate that when used as part of anaesthesia induction with propofol and vecuronium in children, the bolus administration of sufentanil can result in a dose-related attenuation of the cardiovascular intubation response and 0.3 μg kg⁻¹ is the optimal dose of sufentanil to control the cardiovascular intubation response.

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