Intubating conditions and adverse events during sevoflurane induction in infants

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Editor’s key points
- The study evaluated conditions for intubation during sevoflurane induction with or without rocuronium or alfentanil.
- Seventy-five infants were studied in a randomized, placebo-controlled, blinded manner.
- Sixty-three per cent of infants had acceptable intubating conditions with sevoflurane alone.
- Alfentanil added no advantage; rocuronium improved the incidence of acceptable conditions to 92%.

Background. The aim of this study was to compare intubating conditions and adverse events after sevoflurane induction in infants, with or without the use of rocuronium or alfentanil.

Methods. Seventy-five infants, aged 1–24 months, undergoing elective surgery under general anaesthesia were randomly assigned to receive 8% sevoflurane with either placebo (i.v. saline 0.5 ml kg⁻¹), rocuronium (0.3 mg kg⁻¹), or alfentanil (20 μg kg⁻¹). The primary outcome measure was intubating conditions evaluated 90 s after test drug injection by an anaesthetist unaware of the patient’s group. The secondary outcome criteria were respiratory (SpO₂ < 90%, laryngospasm, closed vocal cords preventing intubation, bronchospasm) and haemodynamic adverse events (heart rate and mean arterial pressure variations ≥ 30% control value).

Results. Intubating conditions were significantly better in the rocuronium group, with clinically acceptable intubating conditions in 92%, vs 70% in the alfentanil group and 63% in the placebo group (P = 0.044). Adverse respiratory events were significantly less frequent in the rocuronium group: 0% vs 33% in the placebo group and 30% in the alfentanil group (P = 0.006). Haemodynamic adverse events were more frequent in the alfentanil group: 48% vs 7% in the placebo group and 16% in the rocuronium group (P = 0.0019).

Conclusions. In 1- to 24-month-old infants, the addition of 0.3 mg kg⁻¹ rocuronium to 8% sevoflurane improved intubating conditions and decreased the frequency of respiratory adverse events. Alfentanil provided no additional benefit in this study.

Keywords: anaesthesia; paediatric; complications; hypotension; complications; respiratory; neuromuscular block; rocuronium

Accepted for publication: 15 September 2010

Several methods have been proposed to improve intubating conditions during sevoflurane induction in children. These include clonidine premedication,1 extended exposure to sevoflurane,2 high inspired fraction of sevoflurane,3 addition of nitrous oxide,4 opioids,5 6 or propofol.7 Addition of neuromuscular blocking agents in paediatrics is common in Germany8 and in the USA,9 but it has poorly been studied. Rocuronium has been found to improve intubating conditions in particular situations, such as long exposure to low inspired sevoflurane fraction10 or short exposure (<4 min) to high inspired sevoflurane fraction.11 Most of these studies were conducted in children <2 yr of age. We aimed to study intubating conditions in ≤2 yr old infants, after 8% sevoflurane inhalation with or without either rocuronium or alfentanil. Both respiratory and haemodynamic adverse events were also assessed.

Methods

Patients’ selection

The study protocol was approved by the Ethic Committee and was conducted in compliance with the current revision of the

† J.M.D. and G.M. have equally contributed to this work.
Declaration of Helsinki, the International Conference on Harmonisation guidelines, Good Clinical Practice, and current regulatory guidelines. This prospective, double-blind, randomised, and placebo-controlled study took place in the Fondation Ophtalmologique Adolphe de Rothschild, between November 2005 and May 2006, and included 75 infants. Written informed consent was obtained from the parents or legal guardians. Infants aged 1–24 months, ASA I or II, undergoing elective surgical procedures under general anaesthesia with tracheal intubation, were included. Exclusion criteria were: ASA physical status III or IV, a history of respiratory tract infection in the previous 2 weeks, known or suspected neuromuscular disorders, medication known to interact with rocuronium, a family history of malignant hyperthermia or allergy to any medication used during general anaesthesia, and, finally, anticipated difficult intubation.

Patients were randomized using a computer-generated program, to one of the three study groups undergoing induction of anaesthesia with sevoflurane: 27 patients were randomized to receive placebo (i.v. saline 0.5 ml kg\(^{-1}\)), 23 patients alfentanil 20 \(\mu\)g kg\(^{-1}\), and 25 rocuronium 0.3 mg kg\(^{-1}\). One of the 75 sealed opaque envelopes was opened just before anaesthesia induction to determine the treatment each subject would receive. An independent anaesthetist prepared each treatment.

The infants did not receive any premedication. In the operating theatre, pulse oximetry, ECG, and non-invasive arterial pressure were monitored. Using an appropriate sized facemask via a primed paediatric circle system, all the infants received sevoflurane 8% with 100% oxygen (fresh gas flow 4 litre min\(^{-1}\)). The sevoflurane was maintained at 8% until laryngoscopy. An i.v. cannula was inserted when infants were quiet and pupils central. The 10 ml dilution of the test drugs was prepared by an independent anaesthetist, which was used as a 0.5 ml kg\(^{-1}\) injection (rocuronium 0.6 mg ml\(^{-1}\), alfentanil 40 \(\mu\)g ml\(^{-1}\)). All patients received the study treatments i.v. from a blind assessor according to the random allocation [Time 1 (T1)]. The face-mask ventilation was then assisted using a 10 cm H\(_2\)O inspiratory pressure at a ventilatory frequency of 20 min\(^{-1}\) (anaesthesia machine Primus\textsuperscript{TM}, Dräger France, Antony, France). A direct laryngoscopy was performed 90 s after T1, using a Macintosh size 1 or 2 blade. The trachea was orally intubated with an appropriate sized cuffed tube by a senior paediatric anaesthetist who was unaware of the study treatments, safety assessments, and neuromuscular monitoring. If intubation failed at the first attempt, rocuronium (0.3 mg kg\(^{-1}\)) was injected to allow a second attempt 90 s later.

Intubating conditions were assessed 90 s after T1, by the anaesthetist who performed the tracheal intubation according to the Copenhagen scale\(^{12}\) (Table 1). Intubating conditions were considered clinically acceptable when all the categories scored 1 or 2 (excellent or good) and clinically unacceptable if any category scored 0 (poor). The number of intubation attempts and the duration of intubation (time between the initial introduction of the laryngoscope and the final placement of the tracheal tube and inflation of the cuff in a cuffed tracheal tube) were also recorded. The vocal cords visibility and the need for a cricoid pressure were noted.

The heart rate, the pulse oximetry, and the non-invasive arterial pressure were recorded before the study treatments administration (baseline value) and then every minute for the first 5 min after intubation. Exhaled concentrations of sevoflurane and carbon dioxide were recorded immediately after the placement of the tracheal tube. Haemodynamic adverse events were defined as bradycardia, tachycardia, hypertension, or hypotension (variation ≥ 30% from baseline value). Respiratory adverse events were defined as laryngospasm, closed vocal cords preventing intubation, bronchospasm, or oxygen saturation < 90%.

The visual monitoring of the neuromuscular function at the adductor pollicis muscle was performed using acceleromyography (TOF-Watch; Organon Teknika, Eppelheim, Germany), and was initiated after the induction of anaesthesia but before the administration of the study drug in all the patients. Supramaximal (≥ 35 mA) repetitive TOF stimulation was applied every 15 s at the ulnar nerve via two surface electrodes. Muscle response was assessed until the reappearance of the second twitch of the TOF, allowing a reversal with neostigmine 40 \(\mu\)g kg\(^{-1}\) in combination with atropine 20 \(\mu\)g kg\(^{-1}\). The recovery time (delay between the test drug injection and the reappearance of the second response) was recorded.

### Table 1: Assessment of intubating conditions\(^{11}\)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Clinically acceptable</th>
<th>Clinically not acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laryngoscopy(^{1})</td>
<td>Excellent</td>
<td>Good</td>
</tr>
<tr>
<td>Vocal cords</td>
<td>Easy</td>
<td>Fair</td>
</tr>
<tr>
<td>Position</td>
<td>Abducted</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Movement</td>
<td>None</td>
<td>Moving</td>
</tr>
<tr>
<td>Reaction to the insertion of the tracheal tube</td>
<td>Closed</td>
<td>Closing</td>
</tr>
<tr>
<td>Movements of the limbs</td>
<td>None</td>
<td>Slight</td>
</tr>
<tr>
<td>Coughing</td>
<td>None</td>
<td>Diaphragm</td>
</tr>
</tbody>
</table>

\(\ast\)Intubating conditions. Excellent: all qualities are excellent. Good: all qualities are either excellent or good. Poor: the presence of a single quality listed under ‘poor’. Laryngoscopy. Easy: jaw relaxed, no resistance to blade in the course of laryngoscopy. Fair: jaw not fully relaxed, slight resistance to blade. Difficult: poor jaw relaxation, active resistance of the patient to laryngoscopy.

**Statistical analysis**

A power analysis indicated that 75 patients were required to detect a 60% improvement in the clinically acceptable intubating conditions in the rocuronium group when compared with the placebo and alfentanil groups, with a power of 0.8
and an α error of 0.05. The frequency of clinically acceptable intubating conditions in the rocuronium group was estimated to be 90% based on a previous dose-ranging study in children. The primary outcome of the study was the score of intubating conditions. The secondary outcome criteria were any adverse events.

The intubating conditions and the number of adverse events in the study groups were compared with a χ² test with 2 or 3 degrees of freedom with Yates’ correction as required. Student’s t-test was used to compare the baseline characteristics, the duration of tracheal intubation, the end-tidal carbon dioxide, the end-tidal concentration of sevoflurane, and the sevoflurane exposure time in the three groups. The results are expressed as mean (SD). P-values of <0.05 were considered statistically significant.

**Results**

There were no significant differences between the groups regarding age, weight, ASA physical status, and baseline values of heart rate, arterial pressure, and pulse oximetry (Table 2). Sevoflurane exposure time, end-tidal concentration of sevoflurane, and end-tidal carbon dioxide partial pressure did not differ between the groups, but the duration of tracheal intubation was shorter in the rocuronium group (Table 2). The mean time of neuromuscular block recovery was 22 (16) min.

There were significantly more clinically acceptable intubating conditions in the rocuronium group (rocuronium 92% vs placebo 63% vs alfentanil 70%, P=0.044, χ² test with 3 degrees of freedom) (Table 3). There were also significantly more excellent intubating conditions in the rocuronium group (rocuronium 64% vs placebo 15% vs alfentanil 30%, P=0.0043) (Table 3). Twenty-three of 25 patients in the rocuronium group (92%) were intubated at the first attempt compared with 20 of 27 in the placebo group (74%) and 18 of 23 in the alfentanil group (78%) (P=0.2). Clinically not acceptable intubating conditions were due to closed vocal cords (81%), a prolonged cough (14%), and an active resistance during laryngoscopy (5%). Patient characteristic and induction characteristics were not different between infants with unacceptable intubating conditions (n=19, 25%) and those with acceptable (n=56, 75%). Infants with unacceptable intubating conditions were more likely to have a long duration of tracheal intubation (153 (135) s vs 34 (13) s, P<0.001), two attempts of intubation (10 vs 4, P<0.001), and episodes of S_{O2} < 90% (7 vs 0, n=0.0001). No more than two attempts were required for any patient.

There were significantly more patients with adverse events in the placebo and alfentanil groups than in the rocuronium group (P=0.03) (Table 4). Patients in the rocuronium group had significantly less respiratory adverse events (rocuronium 0% vs placebo 29% vs alfentanil 22%, P=0.02, χ² test) (Table 4). Closed vocal cords preventing intubation were the main cause of adverse respiratory events and occurred in 11 cases. Arterial oxygen desaturation (S_{O2} < 90%) occurred in seven cases. Five of them had closed vocal cords during laryngoscopy and were intubated at the second attempt, and two had an excessive cough. There were significantly more patients with severe haemodynamic adverse events in the alfentanil group (alfentanil 35% vs placebo 7% vs rocuronium 16%, P=0.04) (Table 4). Extubation and postoperative care were uneventful for all infants.

**Discussion**

In this prospective, randomized, double-blind study, involving infants aged 1–24 months, the addition of 0.3 mg kg⁻¹...
rocuronium to 8% sevoflurane improved intubating conditions while the incidence of adverse events was reduced. The alfentanil 20 μg kg⁻¹ increased haemodynamic adverse events and did not improve intubating conditions.

Some studies have demonstrated that neuromuscular blocking agents may improve intubating conditions in >2-yr-old children in particular circumstances. For example, an exposure time to 8% sevoflurane <4 min was associated with a low 30% frequency of good intubating conditions.¹⁰ The frequency reached 100% when 0.3 mg kg⁻¹ rocuronium was added. The same authors found a similar benefit during prolonged exposure to 2% sevoflurane and 50% nitrous oxide.¹² Conversely, Politis and colleagues¹³ did not find any benefit to co-administering 0.25 mg kg⁻¹ rocuronium and 3% halothane, but this study involved a heterogeneous population of 42 children, aged from 3 months to 11 yr. In our single-centre study on 75 infants, involving long exposure and high concentration of sevoflurane, 0.3 mg kg⁻¹ rocuronium provided 92% rate of acceptable intubating conditions and reduced the time to achieve intubation.

Sevoflurane is known to provide adequate intubating conditions in children.¹⁻³¹⁴ In the present study, the rate of poor intubating conditions reached 37% in the sevoflurane-placebo group, despite a long exposure to 8% sevoflurane [10 (2) min]. This result may be partly explained by the use in our study of the criteria defined in the recent recommendations on good clinical research practice on intubation.¹¹ These criteria do not consider only the mobilization of the shoulders, but also the vocal cords position and mobility (Table 1). As previously described in other studies in children,¹⁴¹⁵ closed vocal cords were the main cause of poor intubating conditions in the present study. Another explanation is that many studies reporting good intubating conditions with sevoflurane have investigated for the effective-concentration for 50% of the children (EC50%) or the effective-exposure time at a fixed concentration, using the Dixon’s up-and-down method.¹⁻⁶ Nevertheless, the Dixon’s up-and-down method used to assess EC50% is known for its imprecise value in estimating the clinician’s main interest, that is, the EC90%.¹⁶ Finally, all the studies demonstrating good intubating conditions with sevoflurane alone,¹⁴⁻¹⁷ included ≥3-yr-old children. The present results, like others, suggest that these good intubating conditions may not be expected in infants or neonates.¹⁵¹⁸

Opioids are widely used in children to reduce the cardiovascular response to laryngoscopy and to improve intubating conditions. For example, sufentanil 1 μg kg⁻¹ added to 8% sevoflurane improved intubation conditions.¹⁹ Remifentanil has also demonstrated its effectiveness, but it caused significant haemodynamic effects and required previous injection of atropine.⁵ In the present study, the addition of alfentanil (20 μg kg⁻¹), which is commonly used to intubate,¹⁰ did not significantly improve intubating conditions and did not reduce the incidence of respiratory adverse events, but it increased the number of haemodynamic events (Table 4).

Respiratory adverse events remain frequent in paediatrics, especially in <2-yr-old children.²¹⁻²⁵ Twenty-seven of 75 infants in the study (36%) experienced an adverse event. Half of these adverse events were respiratory complications. This prevalence was high, although it is admitted that young age is a risk factor for perioperative events.²¹ Indeed, in a prospective study on 24 165 consecutive paediatric anaesthetics, the reported prevalence of perioperative events was only 3%, half being of respiratory cause.²⁴ However, the rate of respiratory complications was higher in some other series. For example, in a prospective study on 1078 children aged from 1 month to 18 yr, Tait and colleagues²² reported 18–30% perioperative respiratory adverse events, depending on the absence or presence of an upper airway infection. Specifically during intubation, the rate of respiratory events was nearly 14% in the group of children with a cold, regardless of age. Finally, in >1-yr-old children, free of upper airway infections, a prospective observational study found a 21% incidence of perioperative respiratory events.²³ It is worth noting that these events were statistically more frequent in <2-yr-old children, if the anaesthetist was inexperienced but also when neuromuscular blocking drugs were not used for intubation.²³ The present study performed by experienced paediatric anaesthetists confirms that rocuronium may reduce respiratory events during sevoflurane induction. Thus, the incidence of respiratory events was, respectively, 30% and 33% in the placebo and alfentanil groups, vs 0% in the rocuronium group. Finally, the presence of poor intubation conditions increased the intubation time, the number of attempts, and the incidence of Sp⁰₂ < 90% episodes.

The non-depolarizing neuromuscular blocking agents are not used in paediatrics for three reasons: doubts about their usefulness to facilitate intubation, the risk of allergy, and their duration of action. Although the study was single-centre and involved a small number of patients, it seems to demonstrate their true

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Details of adverse events in each group. *P&lt;0.05 vs the placebo group; †P&lt;0.05 vs the alfentanil group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 27)</td>
</tr>
<tr>
<td><strong>Respiratory events</strong></td>
<td></td>
</tr>
<tr>
<td>Laryngospasm or closed vocal cords</td>
<td>7</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>0</td>
</tr>
<tr>
<td>Sp⁰₂ &lt; 90%</td>
<td>4</td>
</tr>
<tr>
<td><strong>Haemodynamic events</strong></td>
<td></td>
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<tr>
<td>Hypotension</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
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<tr>
<td>Bradycardia</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
</tr>
<tr>
<td>Patients with respiratory events</td>
<td>9</td>
</tr>
<tr>
<td>Patients with haemodynamic events (n)</td>
<td>2*†</td>
</tr>
<tr>
<td>Patients with adverse events (n)</td>
<td>11</td>
</tr>
</tbody>
</table>
usefulness in infants. Regarding the risk of anaphylactic reactions, it should be remembered that in children, the main cause is latex exposure and that anaphylactic reactions are a rare cause of cardiac arrest. Finally, if the use of low-dose vecuronium minimized recovery time of the neuromuscular block, there was still a great inter-individual variability in the time necessary to obtain a second response after a TOF stimulation (median 22 min, range 3–69 min). Hence, considerations should be given to neuromuscular block monitoring and also risk of prolonged neuromuscular block for short-duration surgery.

In conclusion, in 1- to 24-month-old infants, addition of 0.3 mg kg$^{-1}$ vecuronium to 8% sevoflurane improved intubating conditions and reduced respiratory adverse events. In contrast, alfentanil 20 µg kg$^{-1}$ provided no benefit.

**Conflict of interest**

B.P. has participated in the clinical development of sugammadex as a co-investigator in two Phase III studies funded by MSD, Oss, The Netherlands.

**References**