Dose-related attenuation of cardiovascular responses to tracheal intubation by intravenous remifentanil bolus in severe pre-eclamptic patients undergoing Caesarean delivery

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\textbf{Background.} The optimal dose of remifentanil to attenuate the cardiovascular responses to tracheal intubation in pre-eclamptic patients undergoing Caesarean delivery under general anaesthesia has not been established. We compared the effects of two low doses of remifentanil on the cardiovascular responses to tracheal intubation and neonatal outcomes.

\textbf{Methods.} Forty-eight women with severe pre-eclampsia were randomly assigned to receive either remifentanil 0.5 $\mu$g $\text{kg}^{-1}$ (R0.5 group, $n=24$) or 1 $\mu$g $\text{kg}^{-1}$ (R1.0 group, $n=24$) over 30 s before induction of anaesthesia using thiopental 5 $\text{mg kg}^{-1}$ and succinylcholine 1.5 $\text{mg kg}^{-1}$. Systolic arterial pressure (SAP), heart rate (HR), and plasma catecholamine concentrations were measured. Neonatal effects were assessed using Apgar scores and umbilical cord blood gas analysis.

\textbf{Results.} SAP was decreased by induction of anaesthesia and increased by tracheal intubation in both groups. The peak SAP after intubation was greater in the R0.5 group than in the R1.0 group, whereas it did not exceed baseline values in either group. HR increased significantly above baseline in both groups with no significant differences between the groups. Three subjects in the R1.0 group received ephedrine due to hypotension (SAP $< 90$ mm Hg). Norepinephrine concentrations remained unaltered after intubation and increased significantly at delivery with no significant differences between the groups. Neonatal Apgar scores and umbilical arterial and venous pH and blood gas values were comparable between the groups.

\textbf{Conclusions.} Both doses of remifentanil effectively attenuated haemodynamic responses to tracheal intubation with transient neonatal respiratory depression in pre-eclamptic patients undergoing Caesarean delivery under general anaesthesia. The 1 $\mu$g $\text{kg}^{-1}$ dose was associated with hypotension in three of 24 subjects.

\textbf{Keywords:} anaesthetic techniques; induction; anaesthetic techniques; laryngoscopy; cardiovascular system; effects; complications; intubation tracheal; opioids; remifentanil

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Laryngoscopy and tracheal intubation usually increase arterial pressure and heart rate (HR).\textsuperscript{1} In women with pregnancy-induced hypertension, the cardiovascular response to tracheal intubation is exaggerated.\textsuperscript{2} The abrupt increase in arterial pressure, although transient, can lead to cerebral oedema and haemorrhage, and cardiac failure with pulmonary oedema, increasing morbidity and mortality in both the mother and child.\textsuperscript{3} In addition, an increase in maternal plasma catecholamine concentrations at the induction of anaesthesia for Caesarean delivery can cause uteroplacental vasoconstriction and hence adversely affect the neonate.\textsuperscript{5–8} Therefore, close control of stress responses during induction of anaesthesia for Caesarean delivery can have both fetal and maternal benefits in pre-eclamptic patients.

Remifentanil has been shown to blunt cardiovascular responses to intubation with minimal neonatal respiratory depression in healthy pregnant patients\textsuperscript{9} and also in severe pre-eclamptics.\textsuperscript{10} However, remifentanil 1 $\mu$g $\text{kg}^{-1}$ given immediately before intubation produced severe hypotension in two (9.5%) of 21 severe pre-eclamptic patients,\textsuperscript{10} suggesting that the dosage of remifentanil should be titrated to improve the risk/benefit ratio from a maternal perspective. Certainly, maternal hypotension, which may compromise uteroplacental perfusion, is as much of a concern as elevated arterial pressure in pre-eclamptic patients.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{Parameter} & \textbf{Value} \\
\hline
Systolic arterial pressure (mm Hg) & \\
\hline
Heart rate (beats min$^{-1}$) & \\
\hline
Plasma catecholamine concentration ($\text{ng ml}^{-1}$) & \\
\hline
\end{tabular}
\caption{Cardiovascular responses to tracheal intubation}
\end{table}
The present study compared the effects of remifentanil at 0.5 or 1.0 \( \mu \text{g kg}^{-1} \) on maternal haemodynamic responses to laryngoscopy and tracheal intubation in severe pre-eclamptic patients undergoing Caesarean delivery under general anaesthesia. As secondary outcome measures, surrogate markers of neonatal outcome, umbilical blood gas data, Apgar scores, requirements for resuscitation, and complications were determined.

**Methods**

The study was approved by the Institutional Review Board for Human Studies, and all patients provided written informed consent. A total of 48 women with severe pre-eclampsia undergoing elective or urgent Caesarean delivery under general anaesthesia were enrolled. Pre-eclampsia was regarded as severe if the systolic arterial pressure (SAP) on admission exceeded 160 mm Hg, the diastolic pressure exceeded 110 mm Hg, or both, obtained on at least two separate occasions, or if the patient had symptoms of imminent eclampsia (severe headache, visual disturbance, epigastric pain, hyperreflexia, dizziness and fainting, or vomiting), and proteinuria on urine dipstick was 3+ or worse.

Subjects were randomly allocated to receive either remifentanil 0.5 \( \mu \text{g kg}^{-1} \) (R0.5 group, \( n=24 \)) or 1.0 \( \mu \text{g kg}^{-1} \) (R1.0 group, \( n=24 \)) before induction of anaesthesia. The dose of remifentanil (1 \( \mu \text{g kg}^{-1} \)) was used, as it was effective in modifying the cardiovascular response to tracheal intubation in healthy parturients. Each treatment was prepared in 10 ml of 0.9% saline by a third party, so that the investigators were unaware of the identity. Exclusion criteria included cardiorespiratory diseases, morbid obesity, known fetal anomalies, or patient refusal. Magnesium sulphate (MgSO_4_) 4 g i.v. plus 10 g i.m. was given initially as a loading dose, followed by 1 g h^{-1} as infusion for seizure prophylaxis. I.V. hydralazine 5 mg was given at 20 min intervals for SAP >160 mm Hg or diastolic pressure <110 mm Hg.

All subjects received 30 ml of 0.3 M sodium citrate 15–20 min before induction of anaesthesia. Upon arrival in the operating theatre, routine monitoring devices were applied and subjects were positioned supine with left lateral tilt. A 20 G catheter was placed in a radial artery and connected to a pressure transducer to measure arterial pressure and to collect blood samples.

After adequate preoxygenation for 3 min, subjects received a bolus of remifentanil 0.5 or 1.0 \( \mu \text{g kg}^{-1} \) over 30 s starting at time –2 min. Immediately thereafter, anaesthesia was induced by a rapid-sequence induction with i.v. sodium thiopental 5 mg kg^{-1} given over 20 s and succinylcholine 1.5 mg kg^{-1} given over 5 s. Tracheal intubation was performed at time 0. After connection of the circuit to the tracheal tube, 5% sevoflurane (vaporizer dial concentration) was administered for the first 1 min, and then adjusted to maintain end-tidal concentration at 1.2%. Anaesthesia was maintained with sevoflurane (1.2% end-tidal) and 50% N_2O in oxygen using a circle circuit with a fresh gas flow of 6 litre min^{-1} until the time of delivery. After delivery, fresh gas flow was reduced to 4 litre min^{-1} until the end of surgery. Muscle relaxation was maintained with vecuronium given as an initial bolus of 0.12 mg kg^{-1} within a few minutes of succinylcholine administration, and the lungs were mechanically ventilated to maintain an end-tidal carbon dioxide tension of 4.0–4.5 kPa. Neuromuscular block was controlled by train-of-four monitoring, and additional boluses of vecuronium 1 mg were used to maintain one twitch response during the surgery. Throughout the study, end-tidal concentrations of sevoflurane, N_2O, and carbon dioxide were measured (Capnomac Ultima; GE Healthcare, Helsinki, Finland) and recorded at 1 min intervals.

Immediately after delivery of the neonate, i.v. oxytocin (40 IU in 1000 ml of 0.9% saline solution) as an infusion and fentanyl 3 \( \mu \text{g kg}^{-1} \) as a bolus were administered. Intraoperative hypotension (SAP <100 mm Hg) was treated by increasing i.v. crystalloid infusion initially, followed by ephedrine 8 mg boluses if SAP decreased below 90 mm Hg. Bradycardia occurring after induction, defined as HR <50 beats min^{-1}, was treated with i.v. boluses of atropine 0.5 mg as required.

At completion of surgery, sevoflurane was discontinued and residual neuromuscular block was antagonized using neostigmine and atropine. Ephedrine and atropine requirements and estimated blood loss were recorded.

SAP and HR were recorded by an independent investigator before injection of the study drug (baseline, time = –2 min), just before initiating laryngoscopy and tracheal intubation (time=0), and at 1 min intervals up to 7 min thereafter. Neonatal Apgar scores at 1 and 5 min were assessed by a paediatrician who was unaware of the group assignment.

At delivery, samples of maternal arterial blood and umbilical venous (UV) and arterial (UA) blood from a double-clamped segment of the umbilical cord were drawn for blood gas analysis (Ciba-Corning, Medfield, MA, USA). The baby’s birth weight, SAP, and HR were measured within 10–20 min of delivery.

Maternal arterial blood samples for measurement of plasma catecholamine concentrations were also drawn in prechilled tubes containing EDTA-Na before the induction of anaesthesia (baseline), 1 min after the onset of intubation, and at the time of delivery. Plasma concentrations of norepinephrine and epinephrine were measured in duplicates using high-pressure liquid chromatography as described in our previous study.

**Statistical analysis**

An *a priori* sample size calculation was performed which revealed that 19 subjects in each group would have an 80% power with \( P<0.05 \) to detect a 20% difference in peak SAP at intubation. Normal distribution was determined using the Kologorov–Smirnov test. Data are expressed as number or mean (SD). They were analysed using StatView software version 4.0 (Abacus Concepts, Berkeley, CA, USA). Both between- and within-group comparisons of haemodynamic and catecholamine data were analysed using two-way repeated-measures analysis of variance followed
by Scheffé’s post hoc testing as required. Categorical data were analysed using Fisher’s exact test. Other data were compared between the groups using unpaired Student’s t-test. Baseline values were taken as those values measured at the time –2 min. A P-value of <0.05 was considered statistically significant.

**Results**

Among 55 subjects initially enrolled in the study, seven were excluded: four due to patient refusal, one due to maternal heart disease, and two due to a failure of establishment of an arterial line. The resultant 48 subjects were randomized in equal numbers to the two groups and completed the study without protocol violations (Fig. 1). There were no differences between the groups with respect to maternal age, weight, height, gestational age, amount of blood loss, surgical characteristics, or incidence of MgSO4 and hydralazine therapy (Table 1). Ephedrine was administered to three subjects (12.5%) in the R1.0 group and none in the R0.5 group for the treatment of hypotension (SAP < 90 mm Hg).

Baseline SAP and HR did not significantly differ between the groups. SAP decreased significantly after induction of anaesthesia and increased after intubation (P < 0.05 compared with pre-intubation). The magnitude of increases was greater in the R0.5 group [28 (24) mm Hg] than in the R1.0 group [15 (20) mm Hg] (P = 0.032); however, SAP did not exceed baseline values in either group (Fig. 2). HR increased after induction of anaesthesia in the R0.5 group and remained unaltered in the R1.0 group. In response to tracheal intubation, HR similarly increased in both groups [6 (8) and 6 (14) beats min⁻¹ in the R0.5 and R1.0 groups, respectively] (Fig. 2).

**Table 1** Maternal characteristics. Values are mean (range), mean (SD), or number (%). There were no significant differences between the groups.

<table>
<thead>
<tr>
<th></th>
<th>R1.0 (n=24)</th>
<th>R0.5 (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>32 (25–41)</td>
<td>32 (24–41)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 (9)</td>
<td>78 (17)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160 (4)</td>
<td>160 (4)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>34.6 (3.3)</td>
<td>34.2 (3.1)</td>
</tr>
<tr>
<td>MgSO4 therapy (%)</td>
<td>24 (100)</td>
<td>24 (100)</td>
</tr>
<tr>
<td>Hydralazine (%)</td>
<td>9 (38)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Estimated blood loss (ml)</td>
<td>786 (294)</td>
<td>804 (301)</td>
</tr>
<tr>
<td>Induction-to-delivery interval (min)</td>
<td>10.7 (1.7)</td>
<td>9.8 (2.2)</td>
</tr>
<tr>
<td>Uterine incision-to-delivery interval (s)</td>
<td>115 (61)</td>
<td>106 (42)</td>
</tr>
</tbody>
</table>

Maternal plasma concentrations of catecholamines are shown in Table 2. Baseline norepinephrine and epinephrine concentrations did not differ between the groups. Norepinephrine concentrations remained unchanged by intubation.
in both groups. At delivery, however, norepinephrine concentrations increased, the magnitude of which did not differ between the groups. Plasma concentrations of epinephrine decreased after intubation and increased above baseline between the groups. Plasma concentrations of epinephrine increased, the magnitude of which did not differ in both groups. However, the two UA cord samples with pH 7.2 (7.09 in both) were in the R1.0 group.

Table 4 illustrates the neonatal characteristics and resuscitative measures. Newborn SAP, HR, body weight, and Apgar scores at 1 and 5 min were comparable between the groups. A large proportion of the neonates were preterm with low birth weight and admitted to the neonatal intensive care unit. About 71–88% required resuscitative measures in the first minute after birth, but no cases showed evidence of prolonged neurological insult or damage as determined by the neonatal Neurologic and Adaptive Capacity Scores. Although there were no episodes of apparent respiratory depression in either group after initial resuscitation, two in the R1.0 group and one in the R0.5 group required intubation in the neonatal intensive care unit due to desaturation associated with respiratory distress syndrome.

**Discussion**

A single bolus of either 0.5 or 1 μg kg⁻¹ remifentanil effectively attenuated haemodynamic and catecholamine responses to laryngoscopy and tracheal intubation in severe pre-eclamptics undergoing Caesarean delivery. There was a transient delayed respiratory depression noted in a significant proportion of newborns in both groups and maternal hypotension in three subjects (12.5%) in the R1.0 group. These findings suggest that remifentanil is a useful adjunct during rapid-sequence induction of anaesthesia in parturients for whom marked haemodynamic fluctuations are undesirable. Nevertheless, the incidence of hypotension suggests that a single bolus of remifentanil 0.5 μg kg⁻¹ is superior to 1.0 μg kg⁻¹ to ablate the pressor response to intubation in pre-eclamptics having Caesarean delivery under general anaesthesia.
Remifentanil has been shown to attenuate cardiovascular responses to tracheal intubation during general anaesthesia for Caesarean delivery. However, its optimal dosage to attenuate the response remains to be established. Ngan Kee and colleagues demonstrated that remifentanil 1 μg kg$^{-1}$ as a single bolus in healthy patients undergoing Caesarean delivery was effective in controlling maternal haemodynamic changes after tracheal intubation. However, Draisci and colleagues found that a bolus dose of remifentanil 0.5 μg kg$^{-1}$ followed by an infusion of 0.15 μg kg$^{-1}$ min$^{-1}$ until peritoneal incision was ineffective. In our study, remifentanil 0.5 μg kg$^{-1}$ administered before induction of anaesthesia significantly attenuated the haemodynamic responses to tracheal intubation in patients with severe pre-eclampsia.

The higher efficacy of remifentanil in our study could be accounted for by several factors. First, near-term pregnant patients with pre-eclampsia have been reported to have low blood volume and reduced lean tissue mass, implying a smaller volume of initial distribution for i.v. remifentanil and a smaller vessel-rich compartment. Remifentanil blood concentrations were significantly higher in pigs in which blood volume was reduced by haemorrhage than in normovolaemic controls when the same dose of remifentanil was infused for 10 min. In addition, remifentanil pharmacokinetic parameters are more closely related to lean body mass than to total body weight, implying remifentanil dosing regimens should be based on lean body mass rather than total body weight. The greater efficacy of remifentanil in our study could be attributed to altered pharmacokinetics. An identical dose of remifentanil 0.5 μg kg$^{-1}$ is more likely to be associated with better antinociception in pre-eclamptics than in normal parturients. Secondly, MgSO$_4$ can obtund the pressor response to tracheal intubation in patients with pre-eclampsia. Since all subjects received MgSO$_4$ on the antenatal ward before the operation (Table 1), MgSO$_4$ given before induction of anaesthesia could have enhanced the effects of remifentanil in attenuating the pressor response to tracheal intubation. Thirdly, the subjects received thiopental 4 mg kg$^{-1}$ for induction of anaesthesia in the study of Draisci and colleagues, whereas ours received 5 mg kg$^{-1}$ which may have enhanced the antinociceptive effects of remifentanil in our study.

Apgar scores at 1 min were lower and the incidence of ventilatory support was higher in neonates of the R0.5 group in our study compared with those born in pre-eclamptics who did not receive remifentanil in previous investigations. It is suggested that remifentanil 0.5 μg kg$^{-1}$ administered maternally should depress neonatal respiration, being in agreement with a previous study. In our study, 19 neonates (79%) in the R0.5 group and 18 (75%) in the R1.0 group were preterm. The immaturity of preterm infants can lead to an impaired function of central nervous system and control of breathing. This might have increased the sensitivity to remifentanil, resulting in respiratory depression. Therefore, when pre-eclamptic women given even a small dose of remifentanil are undergoing Caesarean delivery under general anaesthesia, healthcare workers skilled at respiratory resuscitation of neonates should be present at all time.

A clear advantage of 0.5 μg kg$^{-1}$ against 1.0 μg kg$^{-1}$ remifentanil was haemodynamic stability: three patients (12.5%) in the R1.0 group developed maternal hypotension requiring vasopressor therapy, but none in the R0.5 group did. Since the uteroplacental perfusion is impaired in severe pre-eclampsia, further reduction of uterine blood flow associated with hypotension could be deleterious. Indeed, three babies born to mothers who developed excessive hypotension after remifentanil showed low 1 min Apgar scores (<5), although their 5 min Apgar scores recovered to >7, as we have previously observed. These findings indicate that maternal hypotension in pre-eclampsia can directly depress the fetus, increase the fetal susceptibility to respiratory depression from remifentanil, or both.

In our study, base excess was significantly less in the R1.0 group than in the R0.5 group with true fetal acidosis (UA pH 7.09 in both) in two cases in the former, suggesting diminished placental perfusion. Base deficit and lactate measurements correlate significantly and are good indicators of neonatal outcome. However, there were no significant differences between the groups in Apgar scores and umbilical artery pH and gas tensions, both surrogate markers of adequacy of placental perfusion or plasma catecholamine concentrations at delivery. In addition, mean base deficit values were within a normal range in both groups and their difference was very small. Furthermore, the fetal acidosis in the R1.0 group was noted in mothers with non-reassuring fetal status. Therefore, such a small difference in base excess between the two groups appears to be of no clinical significance.

The use of general anaesthesia for Caesarean delivery in the absence of contraindications to regional anaesthesia raises ethical concerns, as the latter might be advantageous for both the mother and baby. In fact, in many countries, neuraxial anaesthesia is the standard for elective Caesarean delivery and has become a preferred technique to provide labour analgesia or anaesthesia for Caesarean delivery even among women with severe pre-eclampsia. However, the complications of general anaesthetic technique for Caesarean delivery were discussed with subjects, all of whom gave their written informed consent to participate in our study. In addition, the indication was a non-reassuring fetal heart trace in several cases of our study, and all anaesthetics were administered by an experienced anaesthetist to minimize risk. The delay in establishing regional anaesthesia would not be ethically justifiable in these patients.

In summary, our study demonstrated that a single bolus of either 1 or 0.5 μg kg$^{-1}$ remifentanil attenuates maternal HR and pressor responses with minimal and transient neonatal respiratory depression during induction of anaesthesia and tracheal intubation in severe pre-eclamptics undergoing Caesarean delivery. The use of remifentanil 1 μg kg$^{-1}$ was, however, associated with maternal hypotension in 15% of patients. A smaller dose (i.e. 0.25 μg kg$^{-1}$) or establishment
of optimal dose using an up-and-down methodology might further resolve the optimal dose.

Conflict of interest
None declared.

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