Effects of remifentanil on cardiovascular and bispectral index responses to endotracheal intubation in severe pre-eclamptic patients undergoing Caesarean delivery under general anaesthesia

K. Y. Yoo1*, C. W. Jeong1, B. Y. Park1, S. J. Kim1, S. T. Jeong1, M. H. Shin2 and J. Lee3

1Department of Anaesthesiology, 2Department of Preventive Medicine and 3Department of Physiology, Chonnam, National University Medical School, 8 Hak-dong, Gwangju 501-190, South Korea

*Corresponding author. E-mail: kyyoo@jnu.ac.kr

Background. We examined the effects of remifentanil on cardiovascular and bispectral index (BIS) responses to tracheal intubation and neonatal outcomes in pre-eclamptic patients undergoing Caesarean delivery under general anaesthesia.

Methods. Forty-two women with severe pre-eclampsia were randomly assigned to receive either remifentanil 1 μg kg\(^{-1}\) (n=21) or saline (n=21) over 30 s before induction of anaesthesia using thiopentone 4 mg kg\(^{-1}\) and suxamethonium 1.5 mg kg\(^{-1}\). Mean arterial pressure (MAP), heart rate (HR) and BIS values as well as plasma catecholamine concentrations were measured. Neonatal effects were assessed using Apgar scores and umbilical cord blood gas analysis.

Results. Induction with thiopentone caused a reduction in MAP and BIS in both remifentanil and control groups. Following the tracheal intubation MAP and HR increased in both groups, the magnitude of which was lower in the remifentanil group. BIS values also increased, of which magnitude did not differ between the groups. Norepinephrine concentrations increased significantly following the intubation in the control, while remained unaltered in the remifentanil group. The neonatal Apgar scores at 1 min were significantly lower in the remifentanil group than in the control. However, Apgar scores at 5 min, and umbilical artery and vein blood gas values were similar between the groups.

Conclusions. These results suggest that a single bolus of 1 μg kg\(^{-1}\) remifentanil effectively attenuates haemodynamic but not BIS responses to tracheal intubation in pre-eclamptic patients undergoing Caesarean delivery under general anaesthesia. However, its use was associated with maternal hypotension and neonatal respiratory depression requiring resuscitation.


Keywords: anaesthetic techniques, induction; anaesthetic techniques, laryngoscopy; cardiovascular system, effects; complications, intubation tracheal; monitoring, bispectral index; opioids, remifentanil

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Opioids have been successfully used to attenuate the haemodynamic and catecholamine responses following tracheal intubation.\textsuperscript{5, 10–14} Among them, remifentanil, a potent, synthetic \(\mu\)-receptor agonist, has an extremely short duration of action.\textsuperscript{15} Its context-sensitive half-time is 3 min, which is consistent regardless of duration of the infusion.\textsuperscript{16} Although remifentanil may thus be ideal to reduce the risk of neonatal respiratory depression after Caesarean delivery, its use may be limited in pre-eclampsia.\textsuperscript{17} The bispectral index (BIS) has been used successfully to identify the arousal associated with noxious stimulation.\textsuperscript{2} Since remifentanil has been also found to suppress the increase of BIS in response to tracheal intubation in a concentration-dependent manner,\textsuperscript{18} it may then reduce the incidence of intraoperative early recall which is high after Caesarean delivery.\textsuperscript{19}

The present study was aimed to examine whether remifentanil would reduce the maternal haemodynamic changes in response to laryngoscopy and endotracheal intubation in severe pre-eclamptic patients undergoing Caesarean delivery under general anaesthesia. As further secondary outcome measures, maternal arousal responses assessed by BIS to tracheal intubation and surrogate markers of neonatal outcome, umbilical blood gas data, Apgar scores, and 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 42 women with severe pre-eclampsia undergoing elective or urgent Caesarean delivery under general anaesthesia were studied. Pre-eclampsia was regarded as severe if the systolic blood pressure (SAP) on admission exceeded 160 mm Hg and/or the diastolic blood pressure (DAP) exceeded 110 mm Hg, obtained on at least two separate occasions, or if the patient had symptoms of imminent eclampsia (namely severe headache, visual disturbance, epigastric pain, hypertension, dizziness and fainting, or vomiting) and proteinuria on urine dipstick was 3+ or worse.

The patients were randomly allocated to receive either remifentanil 1 \(\mu\)g kg\(^{-1}\) (remifentanil group, \(n=21\)) or saline (control group, \(n=21\)) just before the induction of anaesthesia. The dose of remifentanil (1 \(\mu\)g kg\(^{-1}\)) was adopted as it was effective in modifying the cardiovascular response to tracheal intubation in healthy parturients.\textsuperscript{13} Each treatment was prepared up to 10 ml with 0.9% saline (control group, \(n=21\) or \(2\times 1\) 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 suxamethonium administration, and the lungs were mechanically ventilated to maintain an end-tidal carbon dioxide tension of 4.0–4.5 kPa. Neuromuscular blockade was controlled by train-of-four monitoring, and additional boluses of vecuronium 1 mg were administered to maintain one twitch response during the surgical procedure. Throughout the study, the end-tidal concentration of sevoflurane, \(N_2O\) and carbon dioxide were measured using a gas analyzer (Capnomac Ultima; GE Healthcare, Helsinki, Finland) and recorded at 1-min intervals. We also recorded the time of skin incision, uterine incision, and delivery.

Immediately after delivery of the neonate, i.v. oxytocin (20 IU in 500 ml) as an infusion and 3 \(\mu\)g kg\(^{-1}\) fentanyl as a bolus were administered. Intraoperative hypotension, defined as the mean arterial blood pressure (MAP) less than 80 mm Hg, was treated initially by increasing i.v. crystalloid infusion, followed by ephedrine 8 mg boluses by 1 g h\(^{-1}\) as infusion for seizure prophylaxis. Intravenous hydralazine 5 mg was given at 20-min intervals if SAP increased above 160 mm Hg or DAP above 110 mm Hg, and their uses were recorded.

All patients received 30 ml of 0.3 M sodium citrate, 15–20 min prior to induction of anaesthesia. Upon arrival in the operating theatre, routine monitoring devices were applied and the patient was positioned supine with left lateral tilt. A 20-gauge catheter was placed into a radial artery and connected to a pressure transducer to measure blood pressure and to collect blood samples. A standard BIS electrode montage (BIS Sensor-Aspect Medical Systems, Inc., Natick, MA) was applied to the forehead before induction of anaesthesia, and BIS was measured continuously to identify arousal throughout the surgery using a BIS\(^{\text{SP}}\) monitor (model A-2000; 3.31 software version; Aspect Medical Systems Inc., Natick, MA). The anaesthetist controlling the sevoflurane concentration was blinded to the BIS value.

After adequate preoxygenation for 3 min, patients received either a bolus of remifentanil 1 \(\mu\)g kg\(^{-1}\) or an equivalent volume of 0.9% saline over 30 s starting at time \(-2\) min. Immediately after the study drug, anaesthesia was induced by a rapid-sequence induction with i.v. sodium thiopentone 4 mg kg\(^{-1}\) given over 20 s and suxamethonium 1.5 mg kg\(^{-1}\) given over 5 s. Cricoid pressure was applied as consciousness was being lost and tracheal intubation was performed using direct laryngoscopy at time 0. After connection of the circuit to the endotracheal tube, 5% sevoflurane (vaporizer dial concentration) was administered for the first 1 min, and then adjusted to maintain end-tidal concentration at 1%. Anaesthesia was maintained with sevoflurane, adjusted to maintain an end-tidal concentration of 1.0%, 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 suxamethonium administration, and the lungs were mechanically ventilated to maintain an end-tidal carbon dioxide tension of 4.0–4.5 kPa. Neuromuscular blockade was controlled by train-of-four monitoring, and additional boluses of vecuronium 1 mg were administered to maintain one twitch response during the surgical procedure. Throughout the study, the end-tidal concentration of sevoflurane, \(N_2O\) and carbon dioxide were measured using a gas analyzer (Capnomac Ultima; GE Healthcare, Helsinki, Finland) and recorded at 1-min intervals. We also recorded the time of skin incision, uterine incision, and delivery.
if MAP decreased below 70 mm Hg. Bradycardia occurring after induction, defined as heart rate (HR) less than 50 beats min\(^{-1}\), was treated with i.v. boluses of 0.5 mg atropine as required. At completion of surgery, sevoflurane was discontinued and residual neuromuscular block was reversed using neostigmine and atropine. Ephedrine and atropine requirements, and estimated blood loss were recorded.

BIS values, MAP and HR were recorded by an independent investigator before injection of the study drug (baseline, time=−2 min) and just before initiating laryngoscopy and tracheal intubation (time=0) and at 1-min intervals up to 7 min thereafter. BIS values were recorded as the maximum value displayed within each minute. These values were confirmed by downloading data from the electronic memory of the monitor at the end of surgery. Arousal response (defined by an increase in BIS to intubation) was determined by calculating the difference of highest BIS value observed after intubation (for 7 min after intubation) and BIS value measured just before starting laryngoscopy. Neonatal Apgar scores at 1 and 5 min were assessed by a paediatrician who was unaware of group assignment.

At delivery, samples of maternal arterial blood, and umbilical venous (UV) and arterial (UA) blood from a double-clamped segment of umbilical cord were drawn for measurements of blood gas using a Ciba-Corning 278 Blood Gas System blood gas analyzer (Ciba-Corning, Medfield, MA). The baby’s birth weight, SAP, and HR were measured within 10 to 20 min of delivery.

Maternal arterial blood samples for measurement of plasma catecholamine concentrations were drawn before the induction of anaesthesia (baseline), 1 min after the onset of intubation, and at the time of delivery. The samples were collected into prechilled tubes containing EDTA-Na and immediately centrifuged at 3000 rpm for 10 min at 4°C. The plasma was stored at −70°C until assayed. Plasma concentrations of norepinephrine and epinephrine were measured in duplicates by using high-pressure liquid chromatography.\(^20\) The assay sensitivity was 10 pg ml\(^{-1}\), and within-run precision coefficients of variation were 13.5% and 14.2% for norepinephrine and epinephrine, respectively. All patients were interviewed for recall on the first postoperative day using a standardized set of postoperative questions.\(^21\) This included inquiring for the recall of any unpleasant dreams during intubation or surgery as well as explicit memory recall for operative events.

Statistical analysis

An a priori sample size calculation was performed that revealed that 19 patients in each group would have an 80% power with \(P<0.05\) to detect a 15% difference in MAP. Normal distribution was determined using the Kolmogorov-Smirnov test. Data are expressed as number or mean (sd). They were performed using StatView software version 4.0 (Abacus Concepts, Berkeley, CA, USA). Both between and within group comparisons of BIS, 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

There were no differences between the groups with respect to maternal age, weight, height, or gestational age. Blood loss, surgical characteristics, and incidence of MgSO\(_4\) and hydralazine therapy did not differ between the groups (Table 1). Ephedrine was administered in two patients in the remifentanil group for the treatment of hypotension. The results from these two patients were excluded from the calculation of MAP, HR, and BIS values.

Arterial blood pressures and HR are illustrated in Figure 1. Baseline arterial blood pressures and HR did not significantly differ between the groups. Arterial blood pressures decreased significantly after induction of anaesthesia and increased after intubation \((P<0.05\) compared with pre-intubation\()\) in both groups. However, arterial blood pressures in the remifentanil group were significantly lower than that in the control from pre-intubation to 3–4 min after intubation \((P<0.001)\). In patients given remifentanil, SAP and MAP remained below baseline throughout the study period. HR increased after induction of anaesthesia, which was abolished by remifentanil. In response to tracheal intubation, HR increased similarly \((6–10\) beats min\(^{-1}\)\) in both groups; however, the peak values were smaller in the remifentanil group \([94 (18)\) beats min\(^{-1}\]\) than in the control \([113 (16)\) beats min\(^{-1}\]\) \((P<0.01)\).

The BIS values are illustrated in Figure 2. Baseline BIS values were similar between the groups. The BIS values decreased after induction of anaesthesia \([43 (13)\) vs 43 (8)]
in control and remifentanil groups, respectively] and then increased after tracheal intubation and skin incision to maximum value [67 (8) vs 69 (6)]. There were no differences in BIS values between the groups during the whole study period. Nor did the increases in BIS from the pre-intubation to maximal values after tracheal intubation and skin incision (arousal) [24 (12) BIS units vs 26 (8) BIS units] differ between the groups. Sevoflurane concentrations were approximately 1.0% in both groups throughout the study. There were no instances of intraoperative recall in either group.

Maternal plasma concentrations of catecholamines are shown in Table 2. Baseline norepinephrine and epinephrine concentrations did not differ between the groups.

### Table 2 Mean (sd) maternal plasma catecholamine concentrations. PI-1, 1 min post-intubation. *P<0.05 vs baseline

<table>
<thead>
<tr>
<th></th>
<th>Remifentanil (n=19)</th>
<th>Control (n=21)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>573 (460)</td>
<td>562 (260)</td>
<td>0.93</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>124 (95)</td>
<td>114 (148)</td>
<td>0.80</td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI-1 Norepinephrine</td>
<td>501 (323)</td>
<td>758 (287)*</td>
<td>0.01</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>69 (89)*</td>
<td>101 (108)</td>
<td>0.30</td>
</tr>
<tr>
<td>Delivery</td>
<td>849 (595)*</td>
<td>860 (361)*</td>
<td>0.95</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>166 (172)</td>
<td>293 (130)*</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Fig 1 Systolic (SAP), mean (MAP), and diastolic (DAP) arterial blood pressures, and heart rate (HR) in the remifentanil and control groups measured before injection of the study drug [remifentanil (R) or saline, t=−2 min], just before intubation (t=0), maximum response within 1 min after intubation, and every 1 min for 7 min after intubation. Values are mean (sd). *P<0.05 vs baseline (t=−2 min); †P<0.05 vs control group.

Fig 2 Bispectral index (BIS) values in the remifentanil and control groups measured before injection of the study drug [remifentanil (R) or saline, t=−2 min], just before intubation (t=0), and every 1 min for 7 min after intubation. Values are mean (sd). *P<0.05 vs baseline (t=−2 min).
The norepinephrine concentrations increased after intubation in the control while remained unchanged in the remifentanil group, and thus were higher at 1 min after intubation in the control than in the remifentanil group ($P<0.01$). At delivery, however, they increased in both groups and did not differ between the groups. Plasma concentrations of epinephrine decreased after intubation compared with baseline and recovered to baseline value at delivery in the remifentanil group ($P<0.05$), while remained unchanged after intubation and increased above baseline at delivery in the control ($P<0.01$). They were significantly higher in the control than in the remifentanil group at delivery ($P<0.01$).

Maternal arterial, and UV and UA blood gases are shown in Table 3. UV and UA blood gases were not recorded in 3 patients in the remifentanil group and 2 in the control, as inadequate blood samples were obtained from the umbilical cord. Maternal arterial and umbilical cord blood gases at delivery were similar and their values were in the acceptable range$^{23}$ in the two groups.

Table 4 illustrates neonatal characteristics and resuscitative measures. Newborn SAP, HR and body weight were similar between the groups. Apgar scores were significantly lower in the remifentanil group at 1 min ($P<0.05$) than in the control but were similar in the two groups at 5 min. A large proportion of the neonates in both groups were pre-term with low birth weight and thus were higher at 1 min after delivery in the control while remained unchanged in the remifentanil group, and thus were higher at 1 min after delivery in the control as inadequate blood samples were obtained from the umbilical cord. Maternal arterial and umbilical arterial partial pressure of carbon dioxide; $P_{CO_2}$, partial pressure of oxygen

**Table 3** Mean (±) maternal arterial and umbilical blood gases data. $P_{CO_2}$, partial pressure of carbon dioxide; $P_{O_2}$, partial pressure of oxygen

<table>
<thead>
<tr>
<th></th>
<th>Remifentanil (n=18)</th>
<th>Control (n=19)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal arterial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$pH$</td>
<td>7.36 (0.05)</td>
<td>7.33 (0.04)</td>
<td>0.15</td>
</tr>
<tr>
<td>$P_{O_2}$, (mm Hg)</td>
<td>36.8 (4.9)</td>
<td>38.1 (3.8)</td>
<td>0.36</td>
</tr>
<tr>
<td>$P_{CO_2}$, (mm Hg)</td>
<td>168.6 (69.5)</td>
<td>198.3 (70.6)</td>
<td>0.28</td>
</tr>
<tr>
<td>Base deficit (mmol litre$^{-1}$)</td>
<td>−4.1 (2.3)</td>
<td>−4.8 (2.1)</td>
<td>0.37</td>
</tr>
<tr>
<td>Umbilical venous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$pH$</td>
<td>7.31 (0.07)</td>
<td>7.27 (0.09)</td>
<td>0.18</td>
</tr>
<tr>
<td>$P_{O_2}$, (mm Hg)</td>
<td>51.1 (10.6)</td>
<td>53.0 (7.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>$P_{CO_2}$, (mm Hg)</td>
<td>22.1 (7.9)</td>
<td>19.6 (5.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Base deficit (mmol litre$^{-1}$)</td>
<td>−2.0 (2.5)</td>
<td>−3.2 (2.8)</td>
<td>0.21</td>
</tr>
</tbody>
</table>
| **Table 4** Neonatal characteristics and resuscitative measures. Values are mean (±) or number (%). SAP, systolic arterial pressure; HR, heart rate

<table>
<thead>
<tr>
<th></th>
<th>Remifentanil (n=21)</th>
<th>Control (n=21)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn SAP (mm Hg)</td>
<td>74 (10)</td>
<td>50 (7)</td>
<td>0.17</td>
</tr>
<tr>
<td>Newborn HR (beats min$^{-1}$)</td>
<td>142 (11)</td>
<td>140 (11)</td>
<td>0.52</td>
</tr>
<tr>
<td>1-min Apgar, &lt;7 (%)</td>
<td>11 (52)</td>
<td>5 (24)</td>
<td>0.11</td>
</tr>
<tr>
<td>Mean</td>
<td>6.1 (2.1)</td>
<td>7.5 (2.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>5-min Apgar, &lt;7 (%)</td>
<td>4 (19)</td>
<td>3 (14)</td>
<td>0.68</td>
</tr>
<tr>
<td>Mean</td>
<td>8.0 (2.1)</td>
<td>8.5 (2.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Resuscitative measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tactile stimulation (%)</td>
<td>7 (33)</td>
<td>7 (33)</td>
<td>1.00</td>
</tr>
<tr>
<td>Bag-mask ventilation (%)</td>
<td>6 (29)</td>
<td>1 (5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Tracheal intubation (%)</td>
<td>5 (24)</td>
<td>4 (19)</td>
<td>0.71</td>
</tr>
<tr>
<td>Total requiring resuscitation (%)</td>
<td>18 (86)</td>
<td>12 (57)</td>
<td>0.04</td>
</tr>
<tr>
<td>Admission to neonatal unit (%)</td>
<td>18 (86)</td>
<td>19 (90)</td>
<td>0.64</td>
</tr>
<tr>
<td>Newborn weight (g)</td>
<td>2076 (754)</td>
<td>1919 (724)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

**Discussion**

The present study demonstrated that a single bolus of remifentanil 1 μg kg$^{-1}$ effectively attenuated haemodynamic and catecholamine but not BIS (arousal) responses to laryngoscopy and tracheal intubation in severe pre-eclamptics undergoing Caesarean delivery, although a transient respiratory depression in a significant proportion of newborns and maternal hypotension were noted. These findings suggest that remifentanil is a useful adjunct during rapid sequence induction of anaesthesia in parturients for whom marked haemodynamic fluctuations are undesirable. However, it should be used with adequate facilities for neonatal respiratory resuscitation.

Pre-eclampsia has been classified as ‘severe’ if blood pressure is greater than 160/110 mm Hg. Tracheal intubation in these patients may provoke life-threatening hypertension leading to cerebral haemorrhage, sudden left ventricular failure and pulmonary oedema.$^{3–5}$ In the present study, peak MAP values were high enough to exceed the upper limit of cerebral autoregulation (130 mm Hg in man)$^{23}$ in 19 (90%) of 21 control patients, in which 9 (43%) had MAP even higher than 160 mm Hg. The changes in maternal MAP and catecholamines in the control group were similar to those reported in a previous study.$^{24}$

Several pharmacologic agents, including vasodilator agents, combined α- and β-adrenergic blocking agents, or opioids, have been used to blunt the hypertensive response to tracheal intubation in severe pre-eclamptics. The relatively slow onset and long duration of action of hydralazine and labetalol prevent rapid adjustment of blood pressure. Sodium nitroprusside and nitroglycerin act rapidly and have a short duration of action. However, they dilate cerebral vasculature$^{25}$ and may increase intracranial pressure especially in severe pre-eclamptics with cerebral oedema. In addition, fetal cyanide toxicity with the use of nitroprusside has been reported in pregnant ewes.$^{26}$ Alfentanil has been shown to be effective in attenuating the hypertensive response to tracheal intubation in

816
pre-eclamptics but its long duration of action may cause prolonged neonatal respiratory depression after Caesarean delivery. Previous studies used remifentanil as a single bolus with or without an infusion to attenuate the cardiovascular response to induction and tracheal intubation. Ngan Kee and colleagues administered remifentanil 1 \( \mu \text{g kg}^{-1} \) as a single bolus in healthy patients undergoing Caesarean delivery under general anaesthesia, and observed that maternal haemodynamics were stable while 2 (10%) neonates had respiratory depression, suggesting that the dosage was too great from a fetal perspective. Other studies also showed that remifentanil is associated with transitory but significant neonatal depression. Since this effect could be dose-dependent, Draisci and colleagues determined whether a low dose remifentanil (a bolus dose of 0.5 \( \mu \text{g kg}^{-1} \) followed by an infusion of 0.15 \( \mu \text{g kg}^{-1} \text{ min}^{-1} \) until peritoneal incision) could control the neuroendocrine response without adverse neonatal outcomes in healthy patients undergoing Caesarean delivery under general anaesthesia. It was shown that maternal haemodynamics were not affected by remifentanil while 3 (14%) neonates required intubation, suggesting that the dosage was too low to attenuate maternal stress responses despite the adversity from a fetal perspective. In our study, the experimental group was pretreated with a single bolus of remifentanil 1 \( \mu \text{g kg}^{-1} \) before induction of anaesthesia, in which the haemodynamic responses to tracheal intubation were significantly reduced with minimal but transient undesirable side-effects. Taken together, remifentanil may be of great clinical benefit to attenuate the stress response in gestational hypertensive patients. However, a further optimization of remifentanil administration protocols is required to improve the risk/benefit ratio for both mother and neonate.

The stress response during the induction of anaesthesia and tracheal intubation may potentially increase fetal risks by raising circulating catecholamine levels and decreasing placental blood flow. Therefore, it was assumed that preventing the increase in the maternal catecholamine concentrations by using remifentanil may improve placental blood flow and neonatal outcomes. In the present study, the plasma norepinephrine concentrations indeed increased significantly at 1 min after tracheal intubation in the control, which was blocked by remifentanil. Nonetheless, there were no significant differences in UA and UV gas and pH values at delivery between the control and remifentanil groups, as previously described. These findings may indicate that maternally administered remifentanil does not provide any beneficial effects, although it is safe from a fetal perspective. The half-time of remifentanil is very short, and the stress response to tracheal intubation lasts less than 5 min. Therefore, beneficial effects of reduced catecholamine responses would be negated until the time of delivery which takes about 9–10 min. Indeed, plasma norepinephrine concentrations did not differ between the groups at the time of delivery.

Opioids may be transferred through the placenta to the neonate, causing respiratory depression during Caesarean delivery. In the present study, 11 neonates (52%) born to mothers given remifentanil showed respiratory depression requiring assisted ventilation immediately after birth. However, remifentanil has similar pharmacokinetics in neonates as in older children and adults. Thus, respiratory depression in the neonate should be transitory as remifentanil is rapidly metabolized. Indeed, all Apgar scores at 5 min except for babies who had respiratory distress syndrome were >7 without naloxone administration, indicating a rapid resolution of respiratory depression. Nonetheless, when remifentanil is used to ablate the haemodynamic responses to maternal laryngoscopy, the presence of health care workers skilled at respiratory resuscitation of neonates appears to be very important.

Babies born to mothers who did not receive remifentanil also required respiratory resuscitative measures frequently immediately after birth. When compared with those born in elective, uncomplicated term pregnancies, the incidence of ventilatory support was higher and Apgar scores were lower at 1 min in neonates of our control group. However, the lower 1-min Apgar scores in the present study are in keeping with the previous study, which showed a lower 1-min Apgar score in severe pre-eclampsia during general anaesthesia than during spinal anaesthesia. This finding probably represents transient sedation from the volatile anaesthetic agents of pre-term infants with or without respiratory distress syndrome. In a recent meta-analysis, general anaesthesia was shown to be associated with transient neonatal sedation. Moreover, the incidence of respiratory distress syndrome is increased in infants of hypertensive mothers. Therefore, all neonates born to pre-eclamptic mothers under general anaesthesia should be monitored for possible immediate, but transient respiratory depression regardless of the use of remifentanil. Alternatively, neuraxial techniques may be used to avoid this unnecessary neonatal respiratory depression in view of recent clinical practice indicating that epidural or spinal anaesthesia can be, and is, safely used, in severely pre-eclamptic women. In fact, regardless of neonatal sedation most anaesthetists would avoid general anaesthesia in the pre-eclamptic secondary to concern for maternal outcome unless regional techniques are contraindicated or failed.

Another major concern in the use of remifentanil in pre-eclamptics undergoing Caesarean delivery is the development of maternal hypotension. Since the uteroplacental perfusion has already been impaired in severe pre-eclampsia, further reduction of uterine blood flow owing to the hypotension should be deleterious. Indeed, two babies born to mothers who developed excessive hypotension after remifentanil showed low 1-min Apgar scores (3 and 4) although their 5-min Apgar scores recovered to

817
7 and 9 and their pH of UA were over 7.2. These findings indicate that maternal hypotension in pre-eclampsia may directly depress the fetus and/or increase the fetal susceptibility to a respiratory depression resulting from remifentanil.

Intraoperative awareness and subsequent recall associated with general anaesthesia may be a disturbing experience after Caesarean delivery. In previous studies, where anaesthesia was induced with thiopentone 4 mg kg$^{-1}$ and maintained with 1% end-tidal sevoflurane with 50% N$2$O (known as the standard general anaesthetic technique for Caesarean delivery for many years), mean BIS values during the period between tracheal intubation and delivery were above 60, which is considered at risk of awareness. Since opioids reduce the BIS response to a painful stimulus, we postulated that remifentanil given before induction may reduce BIS changes and hence the risk of maternal awareness during induction of general anaesthesia. However, BIS values after tracheal intubation did not differ between the groups. This finding suggests that a small dose of remifentanil may not affect BIS responses and the maternal awareness. Nevertheless, it has been shown that clinical sedation significantly increases even with the addition of a small to moderate dose of remifentanil to a sevoflurane anaesthetic even though the BIS does not reflect an increased hypnotic effect. Thus, remifentanil may have the potential to enhance hypnosis and thereby to reduce the occurrence of maternal awareness regardless of the changes in BIS values.

In summary, our study showed that a single bolus of remifentanil 1 $\mu$g kg$^{-1}$ attenuates the maternal HR and blood pressure, while it does not affect the arousal response as measured by BIS during induction of anaesthesia and tracheal intubation. The use of remifentanil was, however, associated with maternal hypotension and neonatal respiratory depression requiring ventilatory support. Although remifentanil is a useful adjunct to improve maternal haemodynamic stability, it should be used with adequate facilities for neonatal respiratory resuscitation. Further studies involving a larger number of high-risk patients such as those with severe pre-eclampsia and different doses of remifentanil with or without infusion are needed.

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