International Journal of Obstetric Anesthesia (2013) 22, 10–18
0959-289X/$ - see front matter
http://dx.doi.org/10.1016/j.ijoa.2012.09.010

ORIGINAL ARTICLE

ELSEVIER
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A dose–response study of remifentanil for attenuation of the hypertensive response to laryngoscopy and tracheal intubation in severely preeclamptic women undergoing caesarean delivery under general anaesthesia

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ABSTRACT
Background: Remifentanil is known to attenuate the cardiovascular responses to tracheal intubation. We determined effective doses (ED_{50}/ED_{95}) of remifentanil to prevent the pressor response to tracheal intubation in patients with severe preeclampsia.
Methods: Seventy-five women with severe preeclampsia were randomly allocated to one of five remifentanil dose groups (0.25, 0.50, 0.75, 1.0, or 1.25 μg/kg) given before induction of anaesthesia using thiopental 5 mg/kg and suxamethonium 1.5 mg/kg. Systolic arterial pressure, heart rate and plasma catecholamine concentrations were measured. Neonatal effects were assessed by Apgar scores and umbilical cord blood gas analysis. A dose was considered effective when systolic arterial pressure did not exceed 160 mmHg for more than 1 min following tracheal intubation.
Results: Baseline systolic blood pressure and heart rate did not differ among the groups. The intubation-induced increases of heart rate and blood pressure were attenuated in a dose-dependent manner by remifentanil. ED_{50} and ED_{95} were 0.59 (95% CI 0.47–0.70) μg/kg and 1.34 (1.04–2.19) μg/kg, respectively. Norepinephrine concentrations remained unaltered following intubation but increased significantly at delivery, with no differences between the groups. Apgar scores and umbilical arterial and venous pH and blood gas values were comparable among the groups. Two women each in the 1.0 and 1.25 μg/kg groups received ephedrine for hypotension defined as systolic arterial pressure <90 mmHg.
Conclusions: The ED_{95} of remifentanil for attenuating the hypertensive response to tracheal intubation during induction of anaesthesia in severely preeclamptic patients undergoing caesarean delivery under general anaesthesia was 1.34 μg/kg.

Keywords: Caesarean; Remifentanil; Hypertension; Tracheal intubation; Preeclampsia

Introduction

Preeclampsia is a complex hypertensive disorder that constitutes a major source of morbidity and mortality worldwide.[1,2] It is characterized by endothelial dysfunction, increased vascular resistance and impaired cerebral autoregulation.[1] The cardiovascular response to tracheal intubation is also markedly exaggerated in these patients, with increases in systemic and pulmonary arterial pressures and pulmonary capillary wedge pressure.[3,4]

Although occurring only in a small proportion of patients with severe preeclampsia, transient but severe hypertension during tracheal intubation has been associated with increased maternal intracranial pressure, cerebral haemorrhage, and cardiac failure with pulmonary oedema, resulting in increased morbidity and mortality in both mother and baby.[5] Moreover, an increase of maternal plasma catecholamine levels upon induction of anaesthesia during caesarean delivery may potentially decrease uterine blood flow[6,7] and hence adversely affect the neonate.[8,9] In particular, preeclampsia is associated with increased sympathetic activity with elevated plasma norepinephrine levels.[10] Thus, close control of stress responses during anaesthesia for caesarean delivery is required in patients with severe preeclampsia.

Remifentanil has a rapid onset with its maximum effect at 1–3 min.[11] It also has a short duration of action, which makes it the most suitable systemic opioid for use in obstetric surgery.[12,13] It has been shown to attenuate the increases in systolic arterial pressure

Accepted September 2012
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(SAP) and heart rate (HR) following induction and tracheal intubation for caesarean delivery during general anaesthesia in healthy pregnant women.[14] Its use, however, may be complicated by neonatal respiratory depression in severely preeclamptic patients.[15,16] The present study was aimed to determine ED_{50} (median effective dose) and ED_{95} (95% effective dose) values of remifentanil to attenuate the pressor response to tracheal intubation during induction of anaesthesia using thiopental 5 mg/kg and suxamethonium 1.5 mg/kg in women with severe preeclampsia. We hypothesized that the use of remifentanil would reduce the maternal stress response to tracheal intubation, with subsequent benefit to the neonate.

Methods

The study was approved by the University Hospital Research Ethics Committee. We enrolled 75 severely preeclamptic but otherwise healthy women who were scheduled to undergo elective or urgent caesarean delivery under general anaesthesia. Informed consent was obtained from each patient. Severe preeclampsia was defined by SAP $\geqslant$160 mmHg and/or diastolic arterial pressure $\geqslant$110 mmHg on admission, or by symptoms of imminent eclampsia (severe headache, visual disturbance, epigastric pain, hyperreflexia, dizziness and fainting, or vomiting) with proteinuria (urine dipstick >300 mg/dL).

Patients were randomly allocated to receive one of five doses of remifentanil, based on a computer-generated randomization list: 0.25 μg/kg (R0.25, $n = 15$), 0.5 μg/kg (R0.5, $n = 15$), 0.75 μg/kg (R0.75, $n = 15$), 1.0 μg/kg (R1.0, $n = 15$), or 1.25 μg/kg (R1.25, $n = 15$). We excluded patients with cardiac or respiratory disease, morbid obesity, diabetes mellitus, three or more previous caesarean deliveries, suspected fetal congenital anomalies and patient refusal. According to our department guidelines, magnesium sulphate ($MgSO_4$) 4 g intravenously plus 10 g intramuscularly was given initially as a loading dose, followed by 1 g/h by infusion for seizure prophylaxis as described previously.[15,16] Intravenous hydralazine 5 mg was given at 20 min intervals for SAP >160 mmHg or diastolic arterial pressure >110 mmHg.

All patients were premedicated with oral 0.3 M sodium citrate 30 mL, 15–20 min before induction of anaesthesia. Upon arrival in the operating room, standard monitoring including electrocardiography, non-invasive arterial pressure, and pulse oximetry was applied, and the patient was positioned supine with 10–15° left lateral tilt. A radial arterial catheter was placed to measure blood pressure and collect blood samples. The bispectral index (BIS) was also monitored using a BIS XP monitor (Model A 2000), with a BIS Quatro™ sensor (Aspect Medical Systems, Natick, MA, USA).

After preoxygenation, the designated dose of remifentanil was given intravenously over 10 s at time −90 s in a double-blinded fashion. Each remifentanil dose was prepared to a total volume of 10 mL with 0.9% saline by a third party, so that the investigators were unaware of the dose. We then immediately performed a rapid-sequence induction using thiopental 5 mg/kg given over 15 s and suxamethonium 1.5 mg/kg given over 5 s. Cricoid pressure was applied and tracheal intubation was performed using direct laryngoscopy at time 0. Anaesthesia was maintained with 1.2% end-tidal sevoflurane and 50% nitrous oxide (N_2O) in oxygen with a fresh gas flow of 6 L/min until the time of delivery. The lungs were mechanically ventilated to maintain end-tidal carbon dioxide (CO_2) tension between 30 and 35 mmHg. Muscle relaxation was maintained with vecuronium as indicated by a peripheral nerve stimulator. Two intravenous cannulae were used, one for remifentanil, the other for injection of other drugs. Throughout the study, end-tidal concentrations of sevoflurane, N_2O and CO_2 were measured using a gas analyzer (Capnomac Ultima, Datex-Ohmeda, Helsinki, Finland) and recorded at 1-min intervals. The times of skin incision, uterine incision, and delivery were also recorded.

After delivery of the baby and umbilical cord clamping, intravenous oxytocin (20 IU in 0.9% saline solution 500 mL) was infused and fentanyl 3 μg/kg was given. Anaesthesia was then maintained using 0.8% end-tidal sevoflurane and 67% N_2O in oxygen, and fresh gas flow was reduced to 4 L/min until the end of surgery. Intraoperative hypotension, defined by SAP <90 mmHg, was treated with intravenous boluses of ephedrine 8 mg. Bradycardia occurring after induction, defined by HR <50 beats/min, was treated with intravenous boluses of atropine 0.5 mg as required. At the end of surgery, sevoflurane was discontinued and residual neuromuscular block was antagonized using neostigmine 0.02 mg/kg and glycopyrrolate 0.004 mg/kg.

BIS values, SAP and HR were recorded by an independent investigator before injection of the study drug (baseline, time −90 s) and just before starting laryngoscopy and tracheal intubation (time 0) and at 1-min intervals up to 7 min thereafter. Episodes of SAP exceeding 160 mmHg for >1 min were also recorded during this period. The success or failure of attenuation of the pressor response to tracheal intubation was the primary outcome of the study. Success was defined if there were no episodes of SAP <160 mmHg for more than 1 min following tracheal intubation. Apgar scores, ephedrine and atropine requirements, and estimated blood loss were also recorded.

At delivery, we collected maternal arterial blood samples for measurement of blood gases using a blood gas analyzer (Ciba-Corning, Medfield, MA, USA). Immediately after delivery of the placenta, we collected samples