Anesthesiology 2006; 104:14–20

Maternal and Neonatal Effects of Remifentanil at Induction of General Anesthesia for Cesarean Delivery

A Randomized, Double-blind, Controlled Trial

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Background: **Use of remifentanil during general anesthesia for cesarean delivery has been described, but its maternal and neonatal effects have not been investigated by a controlled study.**

Methods: **In a randomized, double-blind, controlled study, patients undergoing elective cesarean delivery received an intravenous bolus of 1 μg/kg remifentanil ($n = 20$) or saline ($n = 20$) immediately before induction of general anesthesia. The authors compared maternal hemodynamic changes and neonatal condition and measured plasma concentrations of remifentanil.**

Results: **The maximum increase in systolic arterial pressure from baseline after induction was smaller in the remifentanil group (median, 9 [range, −17 to 31] mmHg) compared with the control group (42 [6–73] mmHg, median difference, 33 mmHg; 95% confidence interval of difference, 23–45 mmHg; $P < 0.0001$). Maximum recorded values were smaller in the remifentanil group compared with the control group for systolic and mean arterial pressure and maternal heart rate. Apgar scores and time to sustained respiration were similar between groups. Two neonates in the remifentanil group were considered clinically depressed at birth and were given a single dose of naloxone. Remifentanil crossed the placenta with an umbilical venous/maternal arterial concentration ratio of 0.73 (SD, 0.17) and an umbilical arterial/umbilical venous concentration ratio of 0.60 (0.23).**

Conclusions: **A single bolus of 1 μg/kg remifentanil effectively attenuated hemodynamic changes after induction and tracheal intubation. However, remifentanil crosses the placenta and may cause mild neonatal depression and thus should be used for clear maternal indications when adequate facilities for neonatal resuscitation are available.**

OPIOID drugs are usually omitted at induction of general anesthesia for cesarean delivery because of the concern that they may cause neonatal respiratory depression. However, in some circumstances, *e.g.*, when there is coexisting maternal disease, increases in maternal heart rate (HR) and arterial blood pressure may be detrimental, and use of an opioid can be justified. Of available opioids, remifentanil may be ideally suited for use in obstetrics because of its rapid metabolism by nonspecific blood and tissue esterases in both mother and neonate. Accordingly, a number of case reports have described the use of remifentanil at induction of general anesthesia in mothers with conditions that include cardiac disease,[1–7] neurologic disease,[8,9] liver disease,[10] and preeclampsia.[11] In the majority of these reports, no adverse effects on neonatal condition at birth were described, leading to suggestions that remifentanil does not cause significant respiratory depression in the neonate.[1,6] However, there have been no controlled studies to support this.

The aim of our study was to compare the maternal and neonatal effects of a single intravenous bolus of 1 μg/kg remifentanil *versus* saline control given at induction of general anesthesia for cesarean delivery. A secondary objective was to assess placental transfer of remifentanil by measuring its plasma concentration in maternal arterial and umbilical cord blood.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

Materials and Methods

This study received approval from the Clinical Research Ethics Committee of the Chinese University of Hong Kong, and all patients gave written informed consent. We recruited 40 women with American Society of Anesthesiologists physical status I or II and term singleton pregnancies who were scheduled to undergo elective cesarean delivery for which general anesthesia had been decided on for clinical reasons. We excluded patients with preexisting or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, a history of substance abuse, or known fetal abnormalities.

Patients were premedicated with 150 mg ranitidine or 20 mg famotidine orally the night before and on the morning of surgery and 0.3 M sodium citrate, 30 ml, on arrival to the operating room. Standard monitoring included noninvasive blood pressure measurement, electrocardiography, and pulse oximetry. We allowed patients to rest undisturbed in the supine position for several minutes, during which blood pressure was measured every 1–2 min. Uterine displacement was achieved

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Received from the Department of Anaesthesia and Intensive Care and the Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong, China. Submitted for publication June 3, 2005. Accepted for publication August 24, 2005. Supported by the Department of Anaesthesia and Intensive Care and the Department of Paediatrics, The Chinese University of Hong Kong. The standard for the remifentanil assay was provided free of charge by GlaxoSmithKline, Middlesex, United Kingdom, who provided no other support or input, financial or otherwise, to this project.

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by tilting the operating table to the left. Blood pressure measurements were continued until they became consistent (three successive measurements of systolic arterial pressure [SAP] that had a difference of no more than 10%). Values for baseline SAP and HR were calculated as the mean of the three recordings. We then inserted a wide-bore intravenous catheter into a forearm vein during local anesthesia and started a slow infusion of lactated Ringer's solution.

We randomly allocated patients to one of two groups by drawing of sequentially numbered sealed envelopes that each contained a computer-generated randomization code. Replacement randomization was used when the codes were generated to ensure equal numbers in each group.[12] For the remifentanil group, 1 μg/kg remifentanil was diluted to a volume of 15 ml with saline in a syringe labeled "study drug." For the control group, 15 ml saline was drawn into an identically labeled syringe. Randomization was performed by an anesthesiologist or investigator who was not involved in patient assessment. The dose of remifentanil we studied was based on data from nonobstetric patients that showed that a bolus of 1 μg/kg was more effective than 0.5 μg/kg for controlling increases in blood pressure and HR after tracheal intubation and caused less hypotension and bradycardia than 1.25 μg/kg.[13]

After preoxygenation, we injected the study drug intravenously over 30 s. We defined the end of injection as time 0 and marked this by starting a stopwatch. We then immediately performed rapid sequence induction. Thiopental, 4 mg/kg, and 1.5 mg/kg succinylcholine were given intravenously, and cricoid pressure was applied. Tracheal intubation was performed using direct laryngoscopy at 1 min. Anesthesia was maintained using isoflurane, adjusted to maintain an end-tidal concentration of 0.5%, and 50% nitrous oxide in oxygen. We ventilated the lungs to maintain an end-tidal carbon dioxide concentration of 32 mmHg. We gave atracurium as required for further muscle relaxation as indicated by a peripheral nerve stimulator. We recorded the times of skin incision, uterine incision, and delivery.

Noninvasive blood pressure was measured at 1-min intervals starting from time 0, and heart rate was measured by electrocardiography. We downloaded all hemodynamic data to a computer at 5-s intervals using software developed within our department. We recorded the maximum and minimal values for SAP, mean arterial pressure (MAP), and HR in the period between induction and uterine incision for each patient.

Hypotension occurring after induction was defined as MAP less than 60 mmHg. This was treated initially by increasing the intravenous fluid infusion followed by 10 mg intravenous ephedrine if more than two consecutive measurements of hypotension occurred. Bradycardia occurring after induction was defined as HR less than 50 beats/min and was treated with intravenous boluses of 0.6 mg atropine as required.

After delivery, the neonate was assessed by a pediatrician (K.C.M.) who was unaware of maternal group assignment. Time to sustained respiration, resuscitative measures required, and Apgar scores 1 and 5 min after birth were recorded. Neonatal resuscitation was performed according to published guidelines.[14] This included the use of tactile stimulation, oxygen insufflation, bag–mask ventilation, tracheal intubation, and suction. According to the guidelines, intramuscular naloxone was indicated by the following criteria: (1) severe respiratory depression after positive-pressure ventilation to restore a normal heart rate and color and (2) history of maternal narcotic administration within the past 4 h. Because of the blinded nature of the study, the second criterion was assumed present for all cases. As a contingency for times when the pediatrician coinvestigator would not be available to attend study cases, the on-call attending pediatric staff were instructed in the study protocol. The decision for admission to the neonatal intensive care unit was according to standard departmental guidelines.

After clamping of the umbilical cord, we gave 0.15 mg/kg morphine and 5–10 U oxytocin intravenously. We then maintained anesthesia using isoflurane adjusted to maintain an end-tidal concentration of 0.3%, and 70% nitrous oxide in oxygen. At the end of surgery, residual neuromuscular block was antagonized using neostigmine and atropine. We provided postoperative analgesia using patient-controlled analgesia. The patient-controlled analgesia device (Abbott Pain Management Provider; Abbott Laboratories, North Chicago, IL) was set to deliver morphine with the following settings: bolus 1 mg, lockout 5 min, 4-h limit 20 mg, and no background infusion.

At the time of delivery, we collected a sample of maternal arterial (MA) blood by radial artery puncture for measurement of plasma concentration of remifentanil. Immediately after delivery of the placenta, we collected samples of umbilical venous (UV) and umbilical arterial (UA) blood from a double-clamped segment of umbilical cord. These samples were used for measurement of the following: (1) blood gases using a Ciba-Corning 278 Blood Gas System blood gas analyzer (Ciba-Corning, Medfield, MA) for patients 1–13 and a Rapidpoint 400 analyzer (Bayer Diagnostics Mfg. [Sudbury] Ltd., Sudbury, United Kingdom) for patients 14–40; (2) oxygen content and total hemoglobin concentration using an IL 682 cooximeter (Instrumentation Laboratory, Lexington, MA) with correction for 70% fetal hemoglobin; and (3) plasma concentration of remifentanil.

Each patient received a routine postoperative follow-up visit on the first day after surgery by an anesthesiologist. In addition, we recorded the total morphine consumption in the first 24 h after operation by down-

loading data from the electronic memory of the patient-controlled analgesia device.

Remifentanil Assay

An assay for remifentanil with a small lower limit of detection was devised for the study by one of the investigators (A.W.). We placed blood samples taken for measurement of remifentanil into tubes containing 20 μl citric acid. The samples were immediately tumble-mixed and flash frozen with liquid nitrogen and then stored at −80°C until analysis. Remifentanil concentration was measured using a liquid chromatography–tandem mass spectrometry system (Applied Biosystems, Boston, MA) in our departmental laboratory. The gradient chromatography was achieved using a reversed phase Hypersil BDS C18 column (ThermoQuest, Runcorn, United Kingdom) with a mobile phase consisting of a mixture of formic acid–acetonitrile and ammonium acetate buffer. Remifentanil concentrations ranging from 0.05 to 20 ng/ml, and fixed amounts of papaverine (internal standard) were spiked into the samples for calculating calibration graphs. During the sample preparation, 0.5 ml of sample (either blank whole blood or patient sample), buffer, and methylene chloride were added. After evaporation of the methylene chloride under nitrogen gas, the residue was reconstituted with 40 μl mobile phase solution, and an aliquot of 30 μl was injected into the system for analysis. The liquid chromatography–tandem mass spectrometry system was operated in the positive ion mode using multiple reaction monitoring with multiple reaction monitoring transitions monitored at m/z 377.4 → 228.1 for remifentanil and m/z 340.3 → 202.0 for papaverine. Interference originating from endogenous compounds in the biologic fluids was not found at the retention times of the analyte and the internal standard. The limit of detection was 0.025 ng/ml based on a signal-to-noise ratio of 3. Linear responses were obtained in analyte/internal standard peak height ratios for analyte concentrations ranging from 0.05 to 20 ng/ml with a correlation coefficient value of 0.9995. Precision and accuracy were assessed by performing analyses on replicate control whole blood samples (0.05, 0.1, 0.5, 1, 5, and 10 ng/ml). The within-day (intraassay) coefficients of variation ranged from 2.84 to 7.81%, and the between-day (interassay) coefficients of variation ranged from 5.20 to 8.27%.

Statistical Analysis

We defined the primary outcome as the maximum increase in SAP from baseline after induction. Using data from our previously published work on hemodynamic changes during cesarean delivery during general anesthesia,[15] we calculated *a priori* that a sample size of 20 patients would have greater than 80% power at the 5% significance level (two tailed) to detect a difference in magnitude of 50% for the maximum increase in SAP in the remifentanil group compared with the control group.

Table 1. Patient Characteristics and Surgical Times

	Remifentanil Group (n = 20)	Control Group (n = 20)	*P* Value
Age, yr	32 (4.9)	34 (5.4)	0.22
Weight, kg	67 (6.6)	67 (9.8)	0.85
Height, cm	156 (8.8)	158 (7.3)	0.40
Induction-to-delivery time, min	12.9 [11.0–14.2]	12.6 [11.2–13.2]	0.44
Uterine incision–to–delivery time, s	80 [53–135]	81 [64–96]	0.73

Values are mean (SD) or median [interquartile range].

Univariate intergroup comparisons were made using the Student *t* test and the Mann–Whitney test as appropriate. Nominal data were analyzed using the chi-square test and Fisher exact test. Serial changes in SAP, MAP, and HR were analyzed using two-way analysis of variance for repeated measures. In this analysis, the independent (qualitative) variable was defined as patient group, and the dependent (quantitative) variable was defined as SAP, MAP, or HR, measured repeatedly over time for each subject. Data were tested for normality using the Kolmogorov-Smirnov test and for sphericity using the Mauchly test. If the Mauchly test was significant, indicating violation of the assumption of sphericity, we used the Greenhouse-Geisser ε adjustment. We used the univariate approach to analyze within-subjects effects. If there was a significant interaction between the between-groups and within-subjects factors (significant treatment × time interaction), we performed simple effects analysis of between-groups factors for all time levels, with Bonferroni adjustments, using a multivariate analysis of variance model. All analyses were performed using Statview for Windows 5.0.1 (SAS Institute Inc., Cary, NC), SPSS for Windows 10.1.4 (SPSS Inc., Chicago, IL) and Confidence Interval Analysis 2.0.0 (T. Bryant, University of Southampton, United Kingdom). Values of $P < 0.05$ were considered significant.

Results

Patient recruitment was completed over a period of 2 yr and 1 month from September 2001 to October 2003. The time required to complete data collection reflects an approximate 8% rate of usage of general anesthesia for elective cesarean delivery in our unit during the study period. The indications for general anesthesia were similar between groups and included placenta previa (24), patient refusal of regional anesthesia (13), and contraindication to regional anesthesia because of anticoagulant therapy or spinal deformity (3). Patient characteristics and surgical details were similar between groups (table 1).

There were no differences between groups in baseline

Table 2. Hemodynamic Changes between Induction and Delivery

	Remifentanil Group (n = 20)	Control Group (n = 20)	*P* Value
Maximum values			
Systolic arterial pressure, mmHg	127 (12.6)	165 (23.0)	< 0.0001
Mean arterial pressure, mmHg	98 (8.6)	123 (15.9)	< 0.0001
Heart rate, beats/min	112 (8.4)	126 (15.4)	0.0008
Minimum values			
Systolic arterial pressure, mmHg	85 (11.4)	102 (19.5)	0.001
Mean arterial pressure, mmHg	55 (16.5)	75 (13.9)	0.0002
Heart rate, beats/min	76 (8.2)	79 (15.7)	0.35
Interventions			
Increased intravenous infusion	2 (10%)	1 (5%)	1.0
Ephedrine required	0 (0%)	0 (0%)	NS
Atropine required	0 (0%)	0 (0%)	NS

Values are mean (SD) or number (%).

NS = not significant.

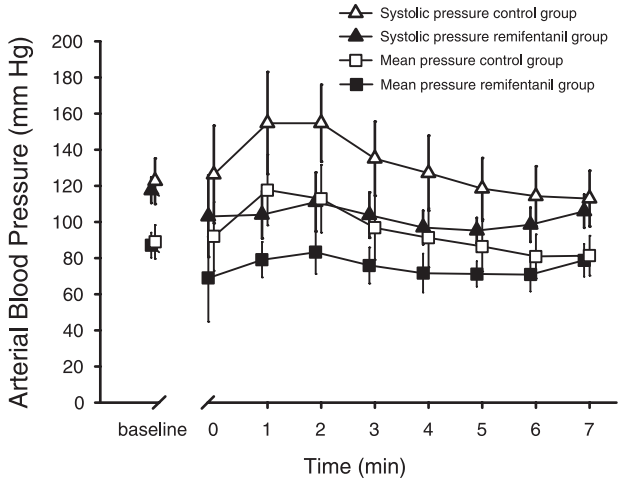

Fig. 1. Serial changes in systolic arterial pressure and mean arterial pressure. There was a significant treatment × time interaction for both systolic and mean arterial pressure ($P < 0.001$). Analysis of between-groups factors for all time levels showed that systolic and mean arterial pressure were greater in the control group *versus* the remifentanil group from 0 to 6 min ($P < 0.05$).

measurements of blood pressure and HR. The primary outcome, the maximum increase in SAP from baseline after induction, was smaller in the remifentanil group (median, 9 [range, −17 to 31] mmHg) compared with the control group (42 [6–73] mmHg; median difference, 33 mmHg; 95% confidence interval of difference, 23–45 mmHg; $P < 0.0001$). Other hemodynamic data are summarized in table 2. The maximum recorded values for SAP, MAP, and HR were smaller in the remifentanil group compared with the control group. The minimum recorded values for SAP and MAP were smaller in the remifentanil group compared with the control group.

Serial changes of SAP, MAP, and HR over time are shown in figures 1 and 2. Because the time from induction to uterine incision varied among patients, serial hemodynamic changes were only compared up to the time of uterine incision of the patient with the smallest induction-to-delivery interval, which was at 7 min. There were no major violations of assumptions of normality, but for all analyses, the Mauchly test of sphericity was significant, and therefore the Greenhouse-Geisser ε adjustment was applied. For SAP, MAP, and HR, there was a significant treatment × time interaction. Analysis of between-groups factors for all time levels showed that SAP was greater in the control group *versus* the remifentanil group from 0 to 6 min, MAP was greater in the control group *versus* the remifentanil group from 0 to 6 min, and HR was greater in the control group *versus* the remifentanil group from 2 to 7 min.

The results of clinical assessment of the neonates are shown in table 3. In five cases, the assessment was made by the on-call pediatrician because the pediatrician coinvestigator was unable to attend. Apgar scores and the number of neonates requiring resuscitative measures were similar between groups. No neonate required tracheal intubation. The median time to sustained respiration was 75 (range, 0–240) s in the remifentanil group *versus* 25 (0–180) s in the control group ($P = 0.28$). Two neonates in the remifentanil group required a single dose of naloxone because they had poor respiratory effort at birth, whereas no neonate in the control group required naloxone ($P = 0.49$). The first neonate who required naloxone had Apgar scores of 6 (1 min) and 10 (5 min) and required a short period of assisted ventilation with onset of sustained respiration after 120 s. The MA and UV plasma concentrations of remifentanil were 0.35 and 0.24 ng/ml, respectively; sufficient blood could not be obtained for measurement of UA remifentanil. The second neonate had Apgar scores of 6 (1 min) and 8 (5 min) and also required a short period of assisted ventilation with onset of sustained respiration after 90 s. The MA, UV, and UA plasma concentrations of remifentanil were 0.40, 0.20, and 0.16 ng/ml, respectively. No

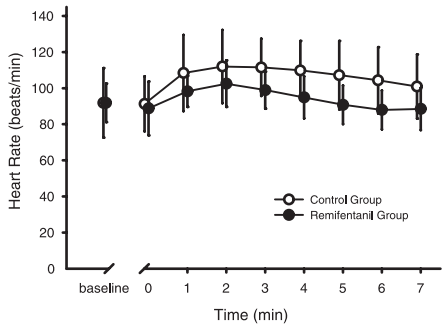

Fig. 2. Serial changes in mean arterial pressure. There was a significant treatment × time interaction ($P < 0.001$). Analysis of between-groups factors for all time levels showed that heart rate was greater in the control group *versus* the remifentanil group from 2 to 7 min ($P < 0.05$).

Table 3. Neonatal Outcome, Resuscitative Measures Required, and Number of and Reasons for Admissions to Neonatal Unit

	Remifentanil Group (n = 20)	Control Group (n = 20)	*P* Value
Apgar scores at 1 min			0.50
7–10	12 (60%)	15 (75%)	
6	6 (30%)	3 (15%)	
5	2 (10%)	2 (10%)	
< 5	0 (0%)	0 (0%)	
Apgar scores at 5 min			NS
8–10	20 (100%)	20 (100%)	
< 8	0 (0%)	0 (0%)	
Time to sustained respiration, s	75 [0–240]	25 [0–180]	0.28
Resuscitative measures			
Tactile stimulation	10 (50%)	6 (30%)	0.20
Bag–mask ventilation	7 (35%)	4 (20%)	0.29
Tracheal intubation	0 (0%)	0 (0%)	1.0
Naloxone	2 (10%)	0 (0%)	0.49
Admission to neonatal unit (number and indication)			NS
Total	3 (15%)	3 (15%)	
Respiratory depression	2 (10%)	0 (0%)	
Maternal medical condition	1 (5%)	3 (15%)	

Values are median [range] or number (%).

NS = not significant.

other factors that may have contributed to neonatal depression were identified in these cases. The induction-to-delivery times were 14.4 and 12.5 min, and the uterine incision-to-delivery times were 45 and 90 s, respectively, and there was no maternal hypotension in either case. Both neonates who were given naloxone were admitted to the neonatal intensive care unit for observation, but there were no sequelae.

Maternal arterial, UV, and UA blood gases; hemoglobin concentration; and oxygen content results are shown in table 4. Sufficient UA blood for analysis could not be obtained in one patient in the remifentanil group. UV partial pressure of carbon dioxide (P_{CO_2}) was slightly

Table 4. Blood Gas Analysis

	Remifentanil Group (n = 20)	Control Group (n = 20)	*P* Value
Umbilical arterial			
pH	7.29 (0.05)	7.29 (0.04)	0.87
P_{CO_2}, mmHg	56 (5.8)	54 (6.1)	0.25
P_{O_2}, mmHg	26 (9.6)	21 (6.7)	0.10
Base excess, mM	−1.1 (2.1)	−2.6 (2.4)	0.06
Total hemoglobin concentration, g/dl	14.1 (1.4)	14.5 (1.3)	0.36
Oxygen content, ml/dl	10.5 (2.8)	9.2 (3.9)	0.23
Umbilical venous			
pH	7.33 (0.04)	7.35 (0.03)	0.29
P_{CO_2}, mmHg	49 (5.6)	46 (3.4)	0.03
P_{O_2}, mmHg	38 (9.5)	36 (10.0)	0.44
Base excess, mM	−1.1 (1.9)	−1.9 (1.5)	0.15
Total hemoglobin concentration, g/dl	14.6 (1.4)	14.8 (1.2)	0.70
Oxygen content, ml/dl	15.7 (2.7)	15.2 (4.0)	0.59

Values are mean (SD) or number (%).

P_{CO_2} = partial pressure of carbon dioxide; P_{O_2} = partial pressure of oxygen.

Table 5. Plasma Concentrations of Remifentanil

	Remifentanil Group (n = 20)
MA, ng/ml	0.32 (0.08)
UV, ng/ml	0.23 (0.06)
UA, ng/ml	0.13 (0.06)
UV/MA ratio	0.73 (0.17)
UA/UV ratio	0.60 (0.23)

Values are mean (SD). Data from one patient were omitted in calculation of umbilical arterial (UA)/umbilical venous (UV) ratio because sufficient blood was not obtained.

MA = maternal arterial.

greater in the remifentanil group (mean, 49 [SD, 5.6] mmHg) compared with the control group (46 [3.4] mmHg). All other measurements were similar between groups.

Maternal arterial, UV, and UA plasma concentrations of remifentanil are shown in table 5. Calculation of the UA/UV ratio excluded data from one patient where sufficient UA blood for analysis could not be obtained. The mean UV/MA remifentanil concentration ratio was 0.73 (95% confidence interval, 0.65–0.81), and the mean UA/UV remifentanil concentration ratio was 0.60 (0.49–0.71).

There was no difference in 24-h morphine consumption by patient-controlled analgesia in the remifentanil group (mean, 30.5 [SD, 19.5] mg) *versus* the control group (27.9 [16.3] mg; $P = 0.64$).

Discussion

Our study showed that, compared with saline control, a single bolus of 1 μg/kg remifentanil given immediately before thiopental and succinylcholine attenuated the increase in blood pressure and HR after induction and tracheal intubation in patients undergoing elective cesarean delivery during general anesthesia. These findings corroborate previous uncontrolled reports of the use of remifentanil in parturients with coexisting disease and confirm that remifentanil is a useful adjunct for general anesthesia in parturients for whom marked hemodynamic fluctuations are undesirable.

However, there is some concern that two neonates of mothers who received remifentanil in our study were given naloxone. Naloxone was also given to neonates in two previous reports when remifentanil was given at cesarean delivery[4,9] and in one report the neonate was born apneic with chest wall rigidity.[10] This shows that, contrary to previous suggestions,[1,6] remifentanil does have the potential to cause a degree of neonatal respiratory depression. However, a number of factors in our study suggest that the degree of respiratory depression from remifentanil at the dose given in our study was mild. Spontaneous respiration was rapidly established in both neonates who received naloxone, and both had Apgar scores of greater than 7 at 5 min. Overall, there was

no difference between groups in time to sustained respiration and Apgar scores, and no neonate in our study required tracheal intubation. Furthermore, as part of our study, it had been emphasized to the attending pediatricians that the mother may have received an opioid on induction; it is possible that this may have influenced their threshold for deciding to give naloxone. Finally, umbilical cord blood concentrations of remifentanil in the two neonates who received naloxone were near the midpoint of the range of values measured in our study, suggesting that other factors were likely to have contributed. Therefore, when there is a clear maternal indication, we would continue to recommend the use of remifentanil provided there is careful evaluation of the potential risks and benefits and adequate preparation for neonatal resuscitation, including attendance by a pediatrician.

Previous reports of remifentanil used at cesarean delivery have described the use of an infusion, with or without a preceding bolus dose. However, there is little evidence to support this as the optimal technique, and it is possible that use of an infusion may contribute to the risk of neonatal depression. For example, Alexander[16] described the use of a bolus dose of 1 μg/kg remifentanil followed by an infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in 6 healthy patients undergoing general anesthesia for cesarean delivery. Using this regimen, maternal blood pressure and HR decreased, 3 patients required glycopyrrolate for bradycardia, and 3 neonates were observed to have respiratory depression, suggesting that the dosage regimen used was too great. Similarly, Van de Velde *et al.*[17] described the use of a bolus dose of 0.5 μg/kg remifentanil followed by an infusion of 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in 10 patients undergoing propofol-based general anesthesia for semielective cesarean delivery. In that report, maternal hypotension occurred in 2 cases, 2 of 13 neonates had Apgar scores of less than 7 at 5 min, and 6 of 13 neonates required assisted ventilation after birth. The possible contribution of propofol to neonatal depression in that report is undetermined.

In contrast, in our study we decided to give only a single bolus of remifentanil immediately before induction. Remifentanil has a rapid onset with maximum effect at 1–3 min[18] and a short duration of action because of rapid metabolism by nonspecific blood and tissue esterases. This makes a single-bolus technique well suited to attenuating the response to a discrete stimulus such as tracheal intubation. For cesarean delivery, we considered this technique to be the best compromise between attenuating the maternal stress response to tracheal intubation and minimizing neonatal plasma concentrations of remifentanil at birth. By avoiding the use of an infusion, neonatal depression at birth should be minimized because of metabolism of the single dose of remifentanil in both maternal and neonatal plasma. However, because two neonates in our study required naloxone, it is possible that the dose we used was excessive. Further dose–response investigations would be of interest.

Should remifentanil be used routinely in general anesthesia for elective cesarean delivery? Normally, after induction of general anesthesia for cesarean delivery without attenuation of the stress response to tracheal intubation, blood pressure and HR may transiently increase to alarmingly high levels in some patients.[15] However, in healthy normotensive patients, this is unlikely to be detrimental and, weighed against the possibility of neonatal depression, argues against the routine use of remifentanil in the dose used in our study. Furthermore, respiratory depression from remifentanil might make it more difficult to establish spontaneous respiration in the mother after failed tracheal intubation. Conversely, induction is associated with increased plasma concentrations of catecholamines,[19] which potentially may decrease uterine blood flow.[20] In previous work, we compared a single bolus of 10 μg/kg alfentanil with control in patients undergoing elective cesarean delivery during general anesthesia.[15] In that study, we found that mothers who received alfentanil had a smaller increase in plasma catecholamine concentration after induction compared with control. This was associated with greater values for UA partial pressure of oxygen (Po_2) in the alfentanil group, raising the possibility of possible fetal benefits from attenuating the maternal stress response. However, because the magnitude of the difference was small and neonates in the alfentanil group had lower Apgar scores, for uncomplicated elective cases, the routine use of alfentanil was not recommended. In comparison, in the current study, we found no significant differences in indices of fetal oxygenation and thus no evidence for a fetal benefit of giving remifentanil. Nonetheless, because there was no difference in Apgar scores between groups, this suggests that if a rapid-acting opioid is required in an obstetric patient, at the doses studied, remifentanil may be a better choice than alfentanil.

In our study, we found that UV Pco_2 was slightly greater in the remifentanil group compared with control. A similar finding was reported by Kan *et al.*,[21] who described the use of a remifentanil infusion during epidural anesthesia for cesarean delivery. The reason for this is unclear. Kan *et al.* explained it by their observation of a slightly increased MA Pco_2, which was consistent with a maternal respiratory depressant effect of remifentanil. However, in our study, this is an unlikely explanation because, although we did not measure MA blood gases, all patients had ventilation controlled during general anesthesia to the same end-tidal carbon dioxide value. An alternative possible explanation is that the increased values for UV carbon dioxide in patients who received remifentanil might reflect a smaller number of neonates in the remifentanil group compared with the control group who had onset of neonatal respiratory effort before the umbilical cord was clamped and may be a further reflection of residual depressant effect of remifentanil. However, the mean difference between groups in our study was small and unlikely to be of clinical significance,

and because we did not measure this variable in our study, the explanation remains speculative.

The concentrations of remifentanil in maternal and umbilical blood in our study were much lower than those reported by Kan *et al.*[21] This reflects differences in dosage and method of administration. Kan *et al.* infused remifentanil at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after establishing an epidural block and deliberately delayed skin incision for at least 15 min to establish a steady state concentration of remifentanil at delivery. This contrasts with our study, in which we gave a single bolus and avoided an infusion with the intention of minimizing maternal and neonatal concentrations at delivery. Our calculated value for the UV/MA ratio of remifentanil (0.73 [SD, 0.17]) is similar to the value reported by Kan *et al.*[21] (0.88 [0.78]) when variability of the data are taken into account. Therefore, our results support the conclusion that remifentanil readily crosses the placenta. However, our value for the UA/UV ratio (0.60 [SD, 0.23]) is greater than that reported by Kan *et al.*[21] (0.29 [0.07]). Therefore, our data support the conclusion that remifentanil undergoes metabolism or redistribution in the neonate but suggest that this occurs to a lesser extent than that suggested by Kan *et al.*

In summary, we have shown that a single bolus of 1 μg/kg remifentanil attenuated the increase in maternal HR and blood pressure after induction of general anesthesia and tracheal intubation. However, remifentanil readily crossed the placenta, and respiratory depression requiring naloxone was observed in two neonates of mothers who received remifentanil. Remifentanil is a useful adjunct for improving maternal hemodynamic stability during general anesthesia for cesarean delivery, but it should be used when there is a clear maternal indication and when adequate facilities for neonatal resuscitation are available.

The authors thank the staff of the Labor Ward (Prince of Wales Hospital, Shatin, Hong Kong, China) for their assistance and cooperation; Anna Lee, M.P.H., Ph.D. (Associate Professor, Department of Anesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong, China), for her assistance with statistical analysis; and Tony Gin, M.B.Ch.B., M.D., F.A.N.Z.C.A., F.R.C.A., F.H.K.A.M. (Professor, Department of Anesthesia and Intensive Care, The Chinese University of Hong Kong), for his input into the study design.

References

1. Scott H, Bateman C, Price M: The use of remifentanil in general anaesthesia for caesarean section in a patient with mitral valve disease. Anaesthesia 1998; 53:695–7

2. Wadsworth R, Greer R, MacDonald JMS, Vohra A: The use of remifentanil during general anaesthesia for caesarean delivery in two patients with severe heart dysfunction. Int J Obstet Anesth 2002; 11:38–43

3. Manullang TR, Chun K, Egan TD: The use of remifentanil for cesarean section in a parturient with recurrent aortic coarctation. Can J Anesth 2000; 47:454–9

4. McCarroll CP, Paxton LD, Elliott P, Wilson DB: Use of remifentanil in a patient with peripartum cardiomyopathy requiring caesarean section. Br J Anaesth 2001; 86:135–8

5. Johnston AJ, Hall JM, Levy DM: Anaesthesia with remifentanil and rocuronium for caesarean section in a patient with long-QT syndrome and an automatic implantable cardioverter-defibrillator. Int J Obstet Anesth 2000; 9:133–6

6. Orme RML'E, Grange CS, Ainsworth QP, Grebinik CR: General anaesthesia using remifentanil for caesarean section in parturients with critical aortic stenosis: A series of four cases. Int J Obstet Anesth 2004; 13:183–7

7. Mertens E, Saldien V, Coppejans H, Bettens K, Vercauteren M: Target controlled infusion of remifentanil and propofol for cesarean section in a patient with multivalvular disease and severe pulmonary hypertension. Acta Anaesthesiol Belg 2001; 52:207–9

8. Bédard JM, Richardson MG, Wissler RN: General anesthesia with remifentanil for cesarean section in a parturient with an acoustic neuroma. Can J Anesth 1999; 46:576–80

9. Imarengiaye C, Littleford J, Davies S, Thapar K, Kingdom J: Goal oriented general anesthesia for cesarean section in a parturient with a large intracranial epidermoid cyst. Can J Anesth 2001; 48:884–9

10. Carvalho B, Mirikitani EJ, Lyell D, Evans DA, Druzin M, Riley ET: Neonatal chest wall rigidity following the use of remifentanil for cesarean delivery in a patient with autoimmune hepatitis and thrombocytopenia. Int J Obstet Anesth 2004; 13:53–6

11. Johannsen EK, Munro AJ: Remifentanil in emergency caesarean section in pre-eclampsia complicated by thrombocytopenia and abnormal liver function. Anaesth Intensive Care 1999; 27:527–9

12. Pocock SJ: Clinical Trials: A Practical Approach. Chichester, John Wiley and Sons, 1983

13. O'Hare R, McAtamney D, Mirakhur RK, Hughes D, Carabine U: Bolus dose remifentanil for control of haemodynamic response to tracheal intubation during rapid sequence induction of anaesthesia. Br J Anaesth 1999; 82:283–5

14. Kattwinkel J: Textbook of Neonatal Resuscitation, 4th edition. Elk Grove Village, Illinois, American Academy of Pediatrics and American Heart Association, 2000

15. Gin T, Ngan Kee WD, Siu YK, Stuart JC, Tan PE, Lam KK: Alfentanil given immediately before the induction of anesthesia for elective cesarean delivery. Anesth Analg 2000; 90:1167–72

16. Alexander R: Haemodynamic changes with administration of remifentanil following intubation for caesarean section [abstract]. Eur J Anaesthesiol 2002; 19 (suppl 24):A571

17. Van de Velde M, Teunkens A, Kuypers M, Dewinter T, Vandermeersch E: General anaesthesia with target controlled infusion of propofol for planned caesarean section: Maternal and neonatal effects of a remifentanil-based technique. Int J Obstet Anesth 2004; 13:153–8

18. Glass PSA, Hardman D, Kamiyama Y, Quill TJ, Marton G, Donn KH, Grosse CM, Hermann D: Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: Remifentanil (GI87084B). Anesth Analg 1993; 77:1031–40

19. Loughran PG, Moore J, Dundee JW: Maternal stress response associated with caesarean delivery under general and epidural anaesthesia. Br J Obstet Gynaecol 1986; 93:943–9

20. Shnider SM, Wright RG, Levinson G, Roizen MF, Wallis KL, Rolbin SH, Craft JB: Uterine blood flow and plasma norepinephrine changes during maternal stress in the pregnant ewe. ANESTHESIOLOGY 1979; 50:524–7

21. Kan RE, Hughes SC, Rosen MA, Kessin C, Preston PG, Lobo EP: Intravenous remifentanil: Placental transfer, maternal and neonatal effects. ANESTHESIOLOGY 1998; 88:1467–74