MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 3806-3813
DOI: 10.12659/MSM.895209

Received: 2015.07.02
Accepted: 2015.08.27
Published: 2015.12.07

Comparative Evaluation of Remifentanil and Dexmedetomidine in General Anesthesia for Cesarean Delivery

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Source of support: Departmental sources

Background: Use of remifentanil and dexmedetomidine in general anesthesia for cesarean section have been described. This study was designed to evaluate the effects of remifentanil and dexmedetomidine on maternal hemodynamics and bispectral index, and neonatal outcomes in elective caesarean delivery.

Material/Methods: Forty-four women undergoing elective cesarean delivery with ASA I or II and term or near-term singleton pregnancies were randomly assigned to receive remifentanil at a loading dose of 2 μg/kg over 10 min followed by a continuous infusion of 2 μg/kg/h until about 6 min before fetal delivery (Group REM), or dexmedetomidine at a loading dose of 0.4 μg/kg over 10 min followed by a continuous infusion of 0.4 μg/kg/h until about 6 min before fetal delivery (Group DEX). Maternal hemodynamics and BIS values were recorded. Neonatal effects were assessed using Apgar scores and umbilical cord blood gas analysis.

Results: Mean arterial pressure (MAP) increased after intubation in both groups, and the change magnitude of the MAP was higher in Group DEX ($P<0.05$). Patients in Group DEX had a lower BIS value at recovery and consumed less propofol during surgery ($P<0.05$). The incidences of neonatal resuscitation at 1 min were 81.8% in Group REM and 54.5% in Group DEX ($P=0.052$). There was no significant difference in either group in Apgar scores at 1 and 5 min and umbilical cord blood gas values.

Conclusions: Both remifentanil and dexmedetomidine are effective to blunt hemodynamic responses to intubation and also seem safe for neonates at the administrated doses, but remifentanil still has the potential to cause neonatal transient respiratory depression.

MeSH Keywords: Anesthesia, General • Cesarean Section • Dexmedetomidine • Narcotic Antagonists

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/895209

3124 3 1 39

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Background

Cesarean section is usually performed under neuraxial anesthesia or general anesthesia. General anesthesia is typically used for cesarean section when neuraxial anesthesia is contraindicated in parturients with coagulation abnormalities, thrombocytopenia, aplastic anemia, vertebral deformity, or local infection, or for emergent situations. Laryngoscopy and tracheal intubation usually increase arterial pressure and heart rate as the results of a reflex increase in sympathetic and sympathoadrenal activity [1]. Opioids are commonly used to attenuate these responses. Nevertheless, because of the risk of neonatal respiratory depression, opioids are usually omitted at induction of general anesthesia for cesarean section.

Remifentanil is a potent, ultra-short-acting μ-receptor agonist with a context-sensitive half-time of 3–5 min, which is consistent regardless of duration of the infusion [2,3]. When general anesthesia is required for cesarean section, remifentanil is an attractive option. It has been shown to blunt hemodynamic responses to intubation in healthy pregnant patients [4,5] and in parturients with severe pre-eclampsia [6–8], but its effects on Apgar scores and the need for airway assist for the neonates have not been defined [9], and the concern that it may cause neonatal respiratory depression still exists.

Dexmedetomidine is a highly selective α2-adrenoceptor agonist, which induces sedation, analgesia, and amnesia without depressing respiratory function [10,11]. Successful use of dexmedetomidine for labor analgesia and/or cesarean section under general anesthesia have been reported in several case reports, if neuraxial anesthesia was contraindicated [12], if the patient refused neuraxial anesthesia [13], or as an adjunct to intravenous opioid-based analgesia if pain relief was not satisfactory [14,15]. Dexmedetomidine sedation for awake fiberoptic intubation was successfully used in a parturient with spinal muscular atrophy for cesarean delivery [16] and in a parturient with Klippel-Feil syndrome [17]. El-Tahan et al. [18] recently showed that preoperative administration of dexmedetomidine at a dose of 0.4–0.6 μg/kg/h over 20 min attenuates maternal hemodynamics and hormonal response to cesarean section without adverse neonatal effects.

However, there have been no controlled studies of remifentanil and dexmedetomidine in cesarean section under general anaesthesia. The aim of our study was to evaluate the effects of remifentanil and dexmedetomidine infused from 10 min before induction of anesthesia to approximately 6 min before fetal delivery on maternal hemodynamics and bispectral index (BIS), and neonatal outcomes in elective caesarean delivery under total intravenous anaesthesia.

Material and Methods

The study was approved by the hospital ethics committee for human studies and all patients provided written informed consent. A total of 44 women with American Society of Anesthesiologists (ASA) physical status I or II and term or near-term singleton pregnancies, scheduled to undergo elective cesarean delivery under general anaesthesia were recruited. The decision to use general anesthesia for cesarean delivery was due to contraindication or patient refusal of neuraxial anesthesia. Exclusion criteria were preexisting or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, a history of substance abuse, allergy to the drugs involved in the study, predicted difficult airway, or known fetal abnormalities.

Subjects were randomly allocated to 1 of 2 groups: Group REM (remifentanil) and Group DEX (dexmedetomidine). Study drugs were prepared by a nurse anesthetist in accordance to the patient's weight in kilograms and blinded to the other members of the anesthesia care team and the patient.

On arrival in the anesthesia room, uterine displacement was achieved by tilting the operating table to the left, a venous line was inserted, 100% oxygen was supplied via face mask, and routine monitoring were established, including noninvasive blood pressure, pulse oximetry, and electrocardiography. Standard BIS electrodes were applied to the patient's forehead before infusion of the study drugs to monitor the BIS of the EEG. Noninvasive blood pressure was measured at 2-min intervals from the initial infusion of the study drugs, at 1-min intervals from the start of anesthesia induction, and at 5-min intervals from the fetal delivery. Mean arterial blood pressures (MAP), heart rate (HR), and BIS value were recorded at several time points as follows: before infusion of the loading dose (baseline), the end of infusion of the loading dose, immediately before laryngoscopy, 1 min after intubation, at skin incision, at uterine incision, immediately after fetal delivery, and 5 min after extubation.

All patients received their study drug in a loading dose at a rate of 0.1 ml/kg over 10 min followed by a continuous infusion at a rate of 0.1 ml/kg/h. Patients in Group REM received remifentanil (0.1 ml/kg at a concentration of 20 μg/ml) at a loading dose of 2 μg/kg over 10 min followed by a continuous infusion of 2 μg/kg/h, while patients in Group DEX received dexmedetomidine (0.1 ml/kg at a concentration of 4 μg/ml) at a loading dose of 0.4 μg /kg over 10 min followed by a continuous infusion of 0.4 μg/kg/h. The continuous infusion was discontinued at about 6 min before fetal delivery.

At the end of infusion of the loading dose, anesthesia was induced with intravenous propofol 2 mg/kg given over 20 s and

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cisatracurium 0.2 mg/kg given over 5 s. Tracheal intubation was performed using direct laryngoscopy 2 min after anesthetic induction. Lungs were mechanically ventilated with 100% oxygen at a tidal volume of 6 ml/kg. Propofol was infused for anesthetic maintenance with BIS values at 40–60. Cisatracurium 0.05 mg/kg was administrated for muscular relaxation as required. After clamping of the umbilical cord, sufentanil 0.3 μg/kg was given to improve analgesia. The times of skin incision, termination of the infusion of the study drugs, uterine incision, and fetal delivery were recorded. Neonatal Apgar scores at 1 and 5 min after fetal delivery were assessed and the need for airway assist, such as tactile stimulation, bag–mask ventilation, and tracheal intubation to the neonate, was recorded. Intramuscular naloxone was given after positive-pressure ventilation to restore a normal HR and skin color if severe respiratory depression occurred.

At delivery, a maternal arterial blood sample was drawn from the radial artery, and umbilical venous (UV) and arterial (UA) blood samples were drawn from a double-clamped segment of umbilical cord for analysis of blood gas.

Hypotension occurring after induction was defined as MAP less than 60 mmHg and was treated by increasing intravenous fluid infusion initially, followed by phenylephrine 0.1 mg boluses if more than 2 consecutive measurements of hypotension occurred. Bradycardia occurring after induction was defined as HR less than 50 beats/min and treated with intravenous boluses of atropine 0.5 mg as required. At the beginning of skin suture, propofol infusion was discontinued and residual neuromuscular block was antagonized using neostigmine and atropine. Extubation time (from termination of propofol infusion to tracheal extubation) was recorded. Postoperative analgesia was provided by delivering sufentanil with the following settings: background infusion 2 μg/h and bolus dose 0.5 μg with lockout time of 15 min.

A routine postoperative follow-up visit was made on the first day after surgery by an anesthetist. Each patient was asked to grade her recall of the procedure (1=none, 2=partial, 3=full) and evaluate her satisfaction with the anesthetic technique (satisfaction score; 0, totally dissatisfied; 10, very satisfied).

Statistical analysis

A prior sample size calculation was performed, which revealed that 21 patients in each group would have an 80% power with $P<0.05$ to detect a 20% difference in MAP. Normal distribution was determined using the Kolmogorov-Smirnov test. Hemodynamic data was analyzed using 2-way repeated measures analysis of variance. Categorical data were analyzed using the chi-square test and Fisher's exact test. Other data were compared between the groups using unpaired Student's t test. Statistical analysis of data was performed with SPSS (Version 13.0, SPSS Inc., Chicago, IL) and a *P* value of less than 0.05 was considered statistically significant.

Results

Patients were recruited from October 2010 to August 2014. The indications for general anesthesia were similar between groups and included patient refusal of neuraxial anesthesia (17 cases) and contraindication to neuraxial anesthesia because of thrombocytopenia (25 cases), spinal deformity (1 case), and local skin infection (1 case). There was no significant difference in patient characteristics and surgical details between groups other than the requirement for propofol during anesthesia maintenance (Table 1). The requirement of propofol during anesthetic maintenance in Group DEX decreased about 40% compared with that in Group REM ($P<0.01$).

MAP, HR, and BIS values are illustrated in Figure 1. There were no differences between groups in the baseline values of MAP, HR, or BIS. At the end of infusion of the loading dose, HR and BIS value decreased significantly in Group DEX compared with the baseline ($P<0.05$), but did not significantly differ between groups. MAP and BIS value decreased significantly after induction of anesthesia in both groups compared with the baseline ($P<0.05$), but there were no differences between groups. MAP increased significantly after intubation in Group DEX compared with that in Group REM ($P<0.05$). MAP, HR, and BIS values did not significantly differ between groups during surgery. At 5 min after tracheal extubation, BIS value was lower in Group DEX than in Group REM [88.4(8.8) *vs.* 93.9(8.2), $P<0.05$]. There were no differences in patient satisfaction with anesthetic technique between groups and intraoperative recall occurred in no cases in either group (Table 1).

The measurement results of the neonates are shown in Table 2. Apgar scores at 1 and 5 min, newborn body weight, and the numbers of neonates requiring resuscitative measures and admission to neonatal care unit were comparable between groups. Neonatal resuscitation at 1 min occurred in 81.8% in Group REM and in 54.5% in Group DEX ($P=0.052$), but there was no evidence of prolonged neurological insult or damage as determined by the neonatal Neurologic and Adaptive Capacity Scores. No episodes of respiratory depression following initial resuscitation arose in neonates from either group. All neonates who were admitted to the neonatal intensive care unit were admitted because of maternal medical condition.

Maternal arterial gases and UV and UA blood gases are summarized in Table 3. UV and UA blood gases were not recorded in 1 patient of Group REM because inadequate blood samples were obtained. Maternal arterial and umbilical cord blood

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Table 1. Maternal characteristics and surgical details.

	REM (n=22)		DEX (n=22)	
Age; yr	28.8	(5.2)	27.6	(5.8)
Weight; kg	66.2	(10.1)	67.3	(8.3)
Height; cm	159.1	(5.4)	160.3	(5.1)
Gestational age; weeks	37.3	(2.3)	36.8	(1.9)
Estimated blood loss; ml	502.3	(247.7)	483.4	(226.1)
Reasons for general anesthesia; number				
Patient refusal to neuraxial anesthesia	8	(36.4%)	9	(40.9%)
Gestational thrombocytopenia	10	(45.5%)	8	(36.4%)
Idiopathic thrombocytopenia	2	(9.1%)	4	(18.2%)
Aplastic anemia	1	(4.5%)	0	(0%)
Lumbar scoliosis	1	(4.5%)	0	(0%)
Skin infection adjacent to the lumbar spine	0	(0%)	1	(4.5%)
Induction-to-delivery interval; min	11.5	(3.2)	12.1	(2.8)
Skin incision-to-delivery interval; min	8.3	(3.4)	8.9	(3.2)
Uterine incision-to-delivery interval; sec	108.2	(49.2)	103.1	(53.3)
Duration of anesthesia; min	68.3	(12.8)	72.7	(13.2)
Requirement of DEX; μg	–		28.7	(3.6)
Requirement of REM; μg	133.7	(19.3)	–	
Requirement of propofol during anesthetic maintenance; mg/kg/hr	5.8	(1.1)	3.9	(0.9)*
Intraoperative intravenous fluid; ml	1066.9	(297.3)	1154.2	(324.6)
Extubation time; min	10.8	(4.5)	11.2	(4.3)
Recall; number				
None	22	(100%)	22	(100%)
Satisfaction score	9.4	(0.6)	9.6	(0.5)

Data are mean (SD), median (range) or number (proportion). * P<0.01 compared with Group REM.

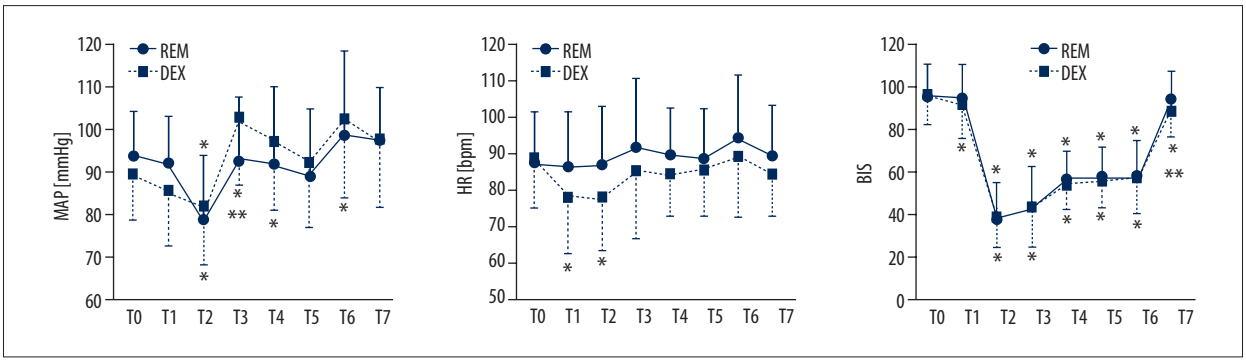

Figure 1. Mean arterial blood pressures (MAP), heart rate (HR) and Bispectral index (BIS) values in Group REM and Group DEX measured before infusion of the loading dose (baseline, T0), at the end of infusion of the loading dose (T1), immediately before laryngoscopy (T2), 1 min after intubation (T3), at skin incision (T4), at uterine incision (T5), immediately after fetal delivery (T6) and 5 min after extubation (T7). REM: remifentanil; DEX: dexmedetomidine. Data are mean ±SD. * *P*<0.05 compared with baseline (T0); ** *P*<0.05 compared with Group REM.

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Table 2. Neonatal outcome, resuscitative measures and reasons of admissions to neonatal unit.

	REM (n=22)		DEX (n=22)	
Apgar scores at 1 min, <7; number	9	(40.9%)	6	(27.3%)
Mean Apgar scores at 1 min	7.3	(2.1)	8.1	(1.8)
Apgar scores at 5 min, <7; number	0	(0%)	1	(4.5%)
Mean Apgar scores at 5 min	8.8	(1.2)	9.2	(0.9)
Newborn weight; g	2854	(533)	2930	(448)
Resuscitation at 1 min; number				
Tactile stimulation	7	(31.8%)	8	(36.4%)
Bag–mask ventilation	11	(50.0%)	4	(18.2%)
Tracheal intubation	0	(0%)	0	(0%)
Naloxone	0	(0%)	0	(0%)
Reasons of admission to neonatal unit; number				
Respiratory depression	0	(0%)	0	(0%)
Maternal medical condition	1	(4.5%)	2	(9.1%)
Total	1	(4.5%)	2	(9.1%)

Data are mean (SD) or number (proportion).

Table 3. Maternal arterial and umbilical blood gases data.

	REM (n=21)		DEX (n=22)	
Maternal arterial				
pH	7.39	(0.04)	7.42	(0.05)*
PCO_2; mm Hg	33.4	(3.4)	33.6	(3.6)
PO_2; mm Hg	437.4	(89.9)	452.2	(91.4)
Base excess; mmol/L	–0.8	(1.8)	–1.4	(2.2)
Umbilical venous				
pH	7.33	(0.04)	7.35	(0.04)
PCO_2; mm Hg	43.4	(4.3)	43.3	(5.2)
PO_2; mm Hg	56.7	(15.4)	58.2	(16.7)
Base excess; mmol/L	–2.1	(2.1)	–1.9	(1.8)
Umbilical arterial				
pH	7.31	(0.04)	7.32	(0.03)
PCO_2; mm Hg	49.2	(5.8)	48.6	(6.3)
PO_2; mm Hg	30.3	(6.2)	32.2	(6.9)
Base excess; mmol/L	–1.5	(2.2)	–1.2	(2.0)

Data are mean (SD). PCO_2 – partial pressure of carbon dioxide; PO_2 – partial pressure of oxygen. * $P<0.05$ compared with Group REM.

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gases at delivery were similar between groups except that pH value of maternal arterial blood was lower in Group REM than that in Group DEX ($P<0.05$).

Discussion

In cesarean section under general anesthesia, it is ideal to minimize maternal stress to tracheal intubation and nociceptive stimuli, and neonatal respiratory depression. Our study showed that there were no differences in Apgar scores, umbilical venous, or arterial blood gas values, and the neonatal neurologic and adaptive capacity scores were similar between the 2 groups. Furthermore, dexmedetomidine was associated with less propofol required in anesthetic maintenance and a deeper level of sedation at recovery, which was similar with the results by Sun et al. [19], who reported that propofol concentrations in a target-controlled infusion model at anesthetic induction and during operation were decreased in patients receiving intramuscular dexmedetomidine as premedication compared with those receiving midazolam.

The positive effect of remifentanil on hemodynamic stability has been shown in previous studies using different doses of remifentanil in healthy pregnant patients [4] and in severe preeclamptics [6–8]. However, its optimal dosage and regimen to blunt the response remains to be established. Park et al. [7] reported that a single bolus of remifentanil at 0.5 μg/kg effectively attenuated hemodynamic response with minimal and transient neonatal respiratory depression in severe preeclamptic patients, while Yoo et al. [6] concluded that the effective doses (ED(50)/ED(95)) of remifentanil to prevent the response were 0.59 and 1.34 μg/kg in severely preeclamptic patients, respectively. However, Draisci et al. [5] found that a bolus dose of remifentanil 0.5 μg/kg followed by an infusion of 0.15 μg/kg/min until peritoneal incision was ineffective in healthy parturients. In our study, remifentanil was infused at 2 μg/kg over 10 min as a loading dose, followed by continuous infusion of 2 μg/kg/h until about 6 min before fetal delivery. Constant mean arterial pressures and heart rates during intubation and operation were observed.

Dexmedetomidine has also been shown to attenuate hemodynamic responses to intubation without harmful neonatal effects in healthy parturients [18]. El-Tahan et al. [18] found that preoperative administration of dexmedetomidine 0.4 and 0.6 μg/kg/h over 20 min was effective in attenuating the maternal hemodynamic response with propofol induction and sevoflurane anesthesia. In our study, dexmedetomidine was infused at 0.4 μg/kg over 10 min as a loading dose, followed by continuous infusion of 0.4 μg/kg/h until about 6 min before fetal delivery. Parturients received dexmedetomidine showed a lower heart rate during intubation and surgery, although there was no significant difference compared with those who received remifentanil. However, the mean arterial pressure at 1 min after intubation was higher in parturients who received dexmedetomidine than that in parturients who received remifentanil, which implied that remifentanil was more effective than dexmedetomidine in blunting cardiovascular response to laryngoscopy and intubation at the doses administered in this study.

Remifentanil crosses the placenta and is cleared rapidly from the neonatal plasma [20]. Its use in cesarean section under general anesthesia was recently systematically reviewed by Heesen et al. [9], but the systematical review failed to define the effects of remifentanil on Apgar scores and the need for airway assist. The current study showed that, although the numbers of neonates requiring resuscitative measures at 1 min were similar between groups, 50% of neonates born to mothers receiving remifentanil showed the need for assisted ventilation, only 18% of those born to mothers receiving dexmedetomidine had this need, which indicated that remifentanil had the disadvantage of causing neonatal transient respiratory depression at the dose administrated in this study.

Dexmedetomidine has a high placental retention [21]. It has shown no significant effect on fetal HR, MAP, blood gas, or cerebral oxygenation in an animal study with pregnant sheep subjected to preterm surgical deliveries [22]. El-Tahan et al. [18] found that Apgar scores, Neurologic and Adaptive Capacity Scores, and acid-base status were similar between the control and the neonates born to mothers receiving preoperative dexmedetomidine 0.2–0.6 μg/kg/h over 20 min. In our study, no differences were found between groups according to the numbers of Apgar scores less than 7 and the mean Apgar scores at 1 and 5 min, and UV and UA pH and gas tensions at delivery; all neonates had Apgar scores more than 7 at 5 min and no neonate required naloxone administration or tracheal intubation. It appears similarly safe for its use with neonates at the dose used in our study.

A high maternal inspired oxygen concentration is helpful to improve fetal oxygenation [23–25]. In the current study, 100% oxygen was supplied, PO_2 values of UV and UA were similar in both groups, and similar with the results of the other studies [24,25]. Many studies used a critical cutoff value for umbilical artery pH of 7.20 [26,27]. Victory et al. [26] found a progression of risk in term infants for Apgar less than 7 at 5 min, including admission to neonatal care unit and need for assisted ventilation with worsening acidosis at birth. Malin et al. [27] clearly defined the role of fetal acidosis by demonstrating that a pH <7.20 increased the risk of morbidity and mortality. In our study, all neonates had an umbilical artery pH of more than 7.20. In addition, maternal artery pH was slightly greater in Group DEX compared with Group REM, but the values were within normal range.

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Intraoperative awareness is a disturbing experience after cesarean section under general anesthesia. It is widely recognized that BIS values between 40 and 60 generally indicate adequate general anesthesia for surgery [28]. Remifentanil had showed no effect on the BIS, even combined with propofol, unless a painful stimulus was applied and a synergistic interaction of hypnosis leading to a propofol-sparing effect [29,30]. Dexmedetomidine produces physiological sleep-like phenomena in the electroencephalogram and a characteristic arousable sedation, which is markedly different from that of other sedatives such as propofol [31]. Kasuya et al. [32] showed that 85% of volunteers had BIS values of 40–60 in those receiving dexmedetomidine only, with the Observer's Assessment of Alertness and Sedation score 3, which was considered an arousable and shallow sedation level. In our study, although the BIS value was lower than the baseline in mothers receiving dexmedetomidine, there were no differences of the BIS values at the end of infusion of the loading dose, or after induction and intubation in groups. In addition, the mothers receiving dexmedetomidine had a lower BIS value at recovery and consumed less propofol during surgery. The findings suggest that dexmedetomidine at the administrated dose has the potential to enhance hypnosis and its effect on BIS responses can be covered by the strong hypnosis of propofol. Chen et al. [33] recently found that dexmedetomidine increased the hypnotic effects of propofol and enhanced the cutoff BIS value of loss of consciousness. This implies that dexmedetomidine has the potential to reduce maternal awareness, but this needs to be demonstrated by further studies.

Aliphatic hydroxylation mediated by the enzyme cytochrome P450 (CYP450) in liver plays a major role in biotransformation and elimination in propofol [34], opioids [35] and dexmedetomidine [36]. Mertens et al. [37,38] found in the combination of propofol and alfentanil, the decreases of elimination clearance and distribution clearance were shown with propofol and with alfentanil, which indicated that there was possibly competitive inhibition of CYP450 activity between propofol and alfentanil. Kharasch et al. [39] reported that dexmedetomidine had a significant potential to inhibit alfentanil biotransformation. Less propofol required in combination with dexmedetomidine as our results and other study [19] showed may be dependent on the mechanism of competitive inhibition of CYP450 activity between propofol and dexmedetomidine. However, there is limited information about the pharmacokinetics of dexmedetomidine and propofol when using together.

There were several limitations in this study. Firstly, this study was a pilot study performed in parturients with ASA I or II and term or near-term singleton pregnancies and without known fetal abnormalities. The regimens of drug use were limited for emergency cesarean section. The nature of the study requires that its results be viewed with caution and studies using larger groups and performed in parturients with obstetrical pathologies such as severe pre-eclampsia are required to confirm the findings. Secondly, the regimens of drug use were different from other studies, so a direct comparison is not feasible. The possible adverse effects of each drug will need to be kept in mind. While the seniority of the study is a limitation, the study still provides clinically useful information for anesthesia providers.

Conclusions

In summary, our study showed that both remifentanil and dexmedetomidine effectively blunt hemodynamic responses to intubation and seem similarly safe for neonates at the administrated doses. Remifentanil still can cause neonatal transient respiratory depression, so dexmedetomidine may be an attractive substitute for remifentanil to maintain hemodynamic stability and minimize neonatal respiratory depression. However, further controlled clinical trials with large samples and in pathological obstetrics are warranted to investigate their safety and efficiency.

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