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Original Article

Propofol in combination with remifentanil for cesarean section: Placental transfer and effect on mothers and newborns at different induction to delivery intervals

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ABSTRACT

Objective: This study aims to describe the administration of propofol in combination with remifentanil for the induction of general anesthesia during cesarean section (CS). Our aim was to evaluate its impact on the drug concentrations of the maternal and neonatal blood at different induction of anesthesia to delivery (I–D) intervals as well as its effect on newborns.

Materials and methods: In this double-blind randomized controlled study, patients undergoing elective CS were administered anesthesia at short (n = 20) or long (n = 20) I–D intervals. Anesthesia was induced with 1 mg/kg propofol and 1 μg/kg remifentanil and maintained by continuous infusion of 3 mg/kg/h propofol and 7 μg/kg/h remifentanil.

Results: The mean plasma propofol concentrations at delivery in the maternal arterial (MA) blood and the fetal umbilical arterial (UA) and venous (UV) blood in the short I–D interval group were 1.91, 1.17, and 0.51 μg/mL, respectively, while those in the long I–D interval group were 1.57, 1.07, and 0.61 μg/mL, respectively. The mean plasma remifentanil concentrations at delivery in the MA, UA, and UV in the short I–D interval group were 2.25, 1.43, and 0.65 ng/mL, respectively, and those in the long I–D interval group were 1.96, 1.25, and 0.75 ng/mL, respectively. There were no statistically significant differences in the neonatal Apgar scores and neurological adaptive capacity scores between the two groups.

Conclusions: It is safe to administer propofol in combination with remifentanil by continuous infusion after the bolus dose for the induction of anesthesia during cesarean section. Prolonging the I–D interval within a certain limit will not have any significant influence on the fetus.

Introduction

Patients with contraindications for regional anesthesia for cesarean section (CS) are anesthetized by general anesthesia, the greatest scruple of which is the effect of anesthetics on the newborns [1]. New and suitable anesthetic agents such as propofol [2–6] and remifentanil [7–11], which have favorable pharmacokinetic profiles and rapid onset and offset durations, have been used previously by various authors, at different dosages and with different methods of administration, for the induction and maintenance of anesthesia, especially in cases of severe maternal cardiovascular and cerebrovascular diseases [12,13], pre-eclampsia [14], hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome [15], in which the blunting of hypertension and tachycardia is believed to be crucial for maternal well-being. In the majority of these reports, no apparent major adverse effects of the anesthetics on the neonatal outcome at birth were described.

Propofol and remifentanil cross the placenta and are cleared from the neonatal circulation rapidly [2,6,7,10,16]. However, in the case reports mentioned above, as well as in several other studies, the plasma levels of the drugs and their potential adverse effects on the newborn at the time of delivery appear to be dependent on the dosage regimens used for induction and maintenance as well as on

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the time lapse between induction of anesthesia and delivery of the newborn. After single administration, propofol and remifentanil have been reported to exhibit transient plasma concentration peaks in mothers, followed by a rapid decline [2,6,7,17,18]. For example, a 2 mg/kg dosage of propofol was reported to appear in the maternal plasma at a peak concentration of 5.01 μg/mL a minute after administration; however, its plasma concentration at delivery, 8.4 min after bolus, was only 1.47 μg/mL [2], which was significantly lower than the minimum plasma concentration (1.64 μg/mL) at which propofol induces unconsciousness in adults [19]. Maintenance of anesthesia by the continuous infusion of remifentanil immediately after the single bolus dose could contribute to the maternal hemodynamic stability and reduce the occurrence of intraoperative awareness [9,20,21]. The combination of propofol and remifentanil has been reported to be more suitable for mothers at high risk of severe hemodynamic fluctuations [22]. Therefore, it is necessary to investigate the optimal method of administration and dosing regimen of these anesthetics during delivery.

In this study, we administered propofol in combination with remifentanil by continuous infusion after single bolus for the induction of general anesthesia for CS and analyzed the maternal and neonatal plasma concentrations of the anesthetics at the time of delivery in order to assess the rate of placental transfer of these two drugs and their effect on the mothers and newborns at different anesthesia induction to delivery (I–D) intervals.

Materials and methods

Study subjects and grouping

This study included 40 parturients with single births, between the ages of 21 and 40 years, pregnant for 37–41 weeks, and requiring elective CS under general anesthesia because of absolute or relative contraindications to regional anesthesia (ASA grades I and II). The exclusion criteria for this study were as follows: the presence of cardiorespiratory diseases, morbid obesity, diabetes, multiple gestation, premature rupture of membranes, and known fetal anomalies. This study was approved by the Ethics Committee of Anhui Provincial Hospital. Written informed consent was obtained from all participants.

We randomly allocated patients to one of two groups by drawing sequentially numbered sealed envelopes that each contained a computer-generated randomization code. Replacement randomization was performed when codes were generated to ensure equal numbers in each group. For the patients of group I, after disinfection and placement of the surgical towels, anesthesia was induced until the BIS of the patient dropped below 60 and consciousness was lost; tracheal intubation and CS were performed simultaneously. For the patients of group II, anesthesia was first induced, followed by disinfection and surgical towel placement.

Anesthetic procedures

All of the patients were orally administered 150 mg ranitidine the night before surgery as well as 2 h before surgery. Upon arrival in the operating room, standard monitoring including electrocardiography and non-invasive arterial pressure and pulse oximetry was applied, and the parturient was positioned supine with a 10–15° left lateral tilt. A radial arterial catheter was placed to measure the blood pressure and collect blood samples. The BIS was continuously monitored using a BIS monitor. An intravenous catheter was inserted into the forearm vein, and lactated Ringer's solution was infused. The patient was provided 6 L/min oxygen for spontaneous breathing until the start of anesthesia induction. Propofol (1 mg/kg; batch no.: JS275, AstraZeneca, Caponago, Italy) and remifentanil (1 μg/kg; batch no.: 6120905, Yichang Humanwell Pharmaceutical Co, Ltd, Hubei) were intravenously injected one after the other within 20–30 s. When the BIS of the patient reached ≤60 and consciousness was lost, 0.8 mg/kg rocuronium was intravenously injected. Following this, endotracheal intubation and mechanical ventilation (tidal volume, 8–10 mL/kg; frequency, 12–15 beats/min) were performed, and the $PetCO_2$ level was maintained at 30–40 mmHg. Immediately after bolus administration, 3 mg/kg/h propofol and 7 μg/kg/h remifentanil were continuously infused to maintain anesthesia, and a low concentration of sevoflurane was provided intraoperatively, if required, according to the depth of anesthesia.

Neonatal assessment

The induction-to-skin incision (I–S), I–D, and uterine incision-to-delivery (U–D) intervals were recorded using a stopwatch. After delivery, the neonatal Apgar score was assessed by a pediatrician blinded to the grouping of the patients, at the following three time points – immediately after delivery, 5 min after delivery, and 10 min after delivery. The concentrations of the gases in the umbilical arterial/venous blood, neonatal weight, necessity and duration of mask ventilation, and necessity for intubation of the newborn were recorded. The neurological adaptive capacity scores (NACS) of the newborns were assessed 15 min, 2 h, and 24 h after delivery.

Sampling and analytical method

Immediately after delivery, 3 mL each of maternal arterial (MA) and fetal umbilical arterial (UA) and venous (UV) blood were extracted. The samples were centrifuged in sodium citrate-coated anticoagulant tubes at 2000 rpm for 10 min, and the plasma was isolated and stored at −70 °C until analysis. The concentration of propofol in the plasma was determined by high performance liquid chromatography with fluorescence detection. The concentration of remifentanil was measured by ultra-performance liquid chromatography tandem mass spectrometry.

Statistical analysis

The statistical analyses were performed using SPSS version 16.0 for Windows. The measurement data were expressed as the mean ± standard deviation ($\bar{x}\pm s$). The concentrations of propofol and remifentanil and the results of the umbilical cord blood gas analysis were compared between the two groups using the Student's t-test. The comparison of the neonatal Apgar scores, NACS, and the resuscitative measures applied were compared between the groups using the chi-square test. The correlation of the I–D intervals with the plasma concentrations of propofol and remifentanil, Apgar scores, and NACS were evaluated in the two groups using the Spearman rank correlation test. Values of $P < 0.05$ were considered as indicating statistical significance.

Results

General information

The contraindications of regional anesthesia were similar between the patients of groups I and II and included placenta previa, refusal of regional anesthesia or contraindication for the same because of coagulation disorders, and presence of spinal deformities. The differences between the two groups in terms of the gestational week, patient age, height, body weight, U-D interval, and infant weight showed no statistical significance, but the I–S