


Prolonged Anesthesia Induction to Delivery Time Did Not Influence Plasma Remifentanyl Concentration in Neonates

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Objective: Remifentanyl, in combination with etomidate and sevoflurane, is commonly used in clinics for general anesthesia induction in cesarean section (CS). This study aimed to evaluate the correlation between the induction to delivery (I-D) time and neonatal plasma drug concentration and anesthesia, as well as its effects on neonates.

Methods: Fifty-two parturients in whom general anesthesia was induced for CS were divided into group A (I-D < 8 min) and group B (I-D ≥ 8 min). Maternal arterial (MA), umbilical venous (UV), and umbilical arterial (UA) blood samples were collected at delivery to analyze the remifentanyl and etomidate concentrations using liquid chromatography-tandem mass spectrometry.

Results: There were no statistically significant differences between the two groups in terms of plasma concentrations of remifentanyl in the MA, UA, and UV blood ($P > 0.05$). The plasma concentration of etomidate in MA and UV was higher in group A than that in group B ($P < 0.05$), whereas the UA/UV ratio of etomidate was higher in group B than that in group A ($P < 0.05$). The Spearman rank correlation test showed no correlation between the I-D time and plasma remifentanyl concentration in the MA, UA, and UV plasma ($P > 0.05$). The concentrations of etomidate in the MA and UV were negatively correlated with the I-D time ($P < 0.05$).

Conclusion: Prolonged I-D time did not significantly influence the maternal or neonatal plasma concentration of remifentanyl. It is safe to administer remifentanyl target-controlled infusion in combination with etomidate and sevoflurane for general anesthesia induction during CS.

Keywords: cesarean section, placental transport, general anesthesia, remifentanyl, etomidate, drug concentration

Introduction

The greatest risk for parturients contraindicated for intraspinal anesthesia for cesarean section (CS) is the side effect of the anesthetics used in the induction of general anesthesia on the neonate.^{1,2} Although the placenta acts as a protective barrier, the degree of protection varies for different drugs and depends on multiple factors, such as lipid solubility, molecular weight, binding to maternal and fetal plasma proteins, and transporter-mediated efflux.³ Opioid analgesics, such as remifentanyl, which have the pharmacokinetic features of rapid onset and offset durations, have been used at different doses with different application methods for anesthesia induction and maintenance in CS. The fentanyl fetus/placenta area under the curve (AUC) ratio has been reported as 39.1%.³ Remifentanyl crosses the placenta and is quickly cleared from neonatal circulation. Pre-delivery remifentanyl administration had no significant effect on the neonatal Apgar scores at 1 and 5 min or respiratory interventions required at birth.⁴ An early study⁵ reported that remifentanyl alone can easily penetrate the placenta when used at low concentrations, and the maternal artery/umbilical arterial (MA/UA) ratio was 0.88. Another study⁶ on the placental transport rate of remifentanyl reported that when combined with propofol, the umbilical venous (UV)/MA ratio was 63%. However, no significant serious adverse effects of the anesthetic drugs on neonatal outcomes at childbirth were reported in most of these studies. Another well-known and widely used

drug for general anesthesia induction in CS is etomidate,⁷ which is cleared rapidly and does not cause myocardial or respiratory depression or hypotension. Notably, etomidate has been reported to have greater advantages for mothers with congenital heart disease previously.^{8,9} According to a previous study, the UV/MA ratio of etomidate was 86%.¹⁰

The potential adverse effects of general anesthetics on neonates depend on the plasma concentration of the drug and maybe the duration between anesthesia induction and delivery. However, there are concerns that a longer interval between anesthesia induction and fetal delivery will lead to higher fetal drug accumulation, thereby resulting in neonatal respiratory depression. Only a limited number of studies have focused on this dilemma. Therefore, this study aimed to analyze the drug concentration in the maternal, UA, and UV blood after the intravenous administration of remifentanyl combined with etomidate for CS and investigate the correlation between plasma concentration and the induction to delivery (I-D) time.

Methods

Study Design

This study was approved by the Research Ethics Committee of the Chongqing Health Center for Women and Children (approval number: 2021-011) and was conducted in accordance with the Declaration of Helsinki. The study was registered at the Chinese Clinical Trial Registry (ChiCTR) (www.chictr.org) (registration ID: ChiCTR2100046547). Informed consent was obtained from all parturients who participated in the study.

Parturients aged 23–42 years with a single birth, at 37–40⁺⁴ weeks of gestation, and requiring elective or emergency CS but contraindicated for intraspinal anesthesia (ASA classification II), who could only be operated under general anesthesia were enrolled in the study. The exclusion criteria were as follows: 1) mental illness, 2) cognitive impairment, 3) high risk of difficult airway, and 4) full stomach requiring conscious tracheal intubation.

Remifentanyl target-controlled infusion (TCI) was administered in combination with a single bolus of etomidate and rocuronium and simultaneous sevoflurane inhalation to induce general anesthesia during CS. The maternal and neonatal blood concentrations of remifentanyl and etomidate immediately after umbilical cord ligation were analyzed to estimate placental transport efficiency. The clinical side effects on the mothers and neonates were recorded. The correlation between plasma anesthetic concentration and I-D time was also evaluated.

Anesthetic Procedure

Electrocardiography (ECG), non-invasive cuff blood pressure, respiration, and pulse oxygen saturation were applied for monitoring the parturient, who was laid supine in a left-leaning position. Before initiating anesthesia induction, oxygen was administered at 5 L/min for spontaneous breathing. TCI of remifentanyl (lot number 10A06191, Yichang Renfu Pharmaceutical Co, Ltd, Hubei) at 5 ng/mL and 5% sevoflurane (lot number: 21052131, Shanghai Hengrui Pharmaceutical Co., Ltd) inhalation was performed simultaneously to induce anesthesia. Etomidate (0.25 mg/kg, lot number: YT210910, Nhwa Pharma. corporation) and rocuronium bromide (0.6 mg/kg, lot number: SE210801, Guangdong Jiabo Pharmaceutical Co., Ltd, Hubei) were administered intravenously with maternal loss of consciousness. Endotracheal intubation was performed, and mechanical ventilation (tidal volume at 8 mL/kg; frequency between 12–15 beats/min) and the end-tidal carbon dioxide partial pressure level (30–40 mmHg) were maintained. The sevoflurane concentration was decreased to 1.5% after administering the muscle relaxant until the fetus was delivered. After umbilical cord ligation, propofol TCI (lot number: RT425, Aspen Pharma Trading Limited) at 3.5 ug/mL and remifentanyl at 5 ng/mL were used for anesthesia maintenance. The Beijing Silugao I-type TCI-infusion pump with built-in Minto pharmacokinetic parameters was used. A neonatal pediatrician was in attendance to meet the neonatal resuscitation needs.

Neonatal Assessment

A stopwatch was used to record three time intervals: induction to skin incision (I-S), uterine incision to delivery (U-D), and I-D time. A midwife and a pediatrician evaluated the Apgar scores of the neonates at three time points: 1 min, 5 min, and 10 min after delivery. The umbilical artery blood gas analysis results, neonatal weight, and resuscitation measures for neonates, including tactile stimulation, bag-mask ventilation, and tracheal intubation, were recorded.

Sampling and Analytical Method

MA, UV, and UA blood samples were obtained at the same time immediately after umbilical cord ligation to analyze the drug concentrations of remifentanyl and etomidate. The samples were collected in anticoagulant tubes with sodium citrate and centrifuged for 10 min at 3000 rpm at 4°C. The centrifuged plasma was isolated and stored at -80°C for further analysis. The concentrations of remifentanyl and etomidate were determined using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). The data were processed and quantified using Mass Lynx Mass Spectrometry Software (Waters, Milford, Massachusetts, USA).

Grouping and Statistical Analysis

The enrolled participants were divided into group A (I-D < 8 min) and group B (I-D ≥ 8 min) according to the I-D time. Since I-D time in most situations is 6.9 ± 1.2 minutes,⁶ the cut-off value was selected as 8 min. Generally, the I-D time in most cases will not exceed 8 min,¹¹ which is close to the unpublished data in our center.

SPSS version 21.0 was used for statistical analyses. Normally distributed data are expressed as mean ± standard deviation ($\bar{X} \pm SD$). The correlation between the interval time and the plasma concentrations of anesthetic drugs was evaluated using the Spearman rank correlation test. The concentrations of remifentanyl or etomidate and other measurement data were compared between the two groups using the Student's *t*-test. Counting data, such as the Apgar scores, were compared using the chi-square test. P-values were set at 0.05, indicating statistical significance.

Results

General Information

Fifty-two parturients were enrolled in this study. The differences in age, height, body weight, body mass index (BMI), gestational week, preoperative complications, preoperative laboratory examination, and I-S interval between the groups showed no statistical significance ($P > 0.05$). The I-D and U-D intervals in group B were significantly longer than those in group A ($P < 0.05$; Table 1).

Indications for Selecting General Anesthesia

General anesthesia was induced due to a history of lumbar disc herniation or lumbar surgery in 44.23% and thrombocytopenia in 30.77% of cases. Table 2 presents the proportion of other causes.

Neonatal Information

No statistically significant differences were observed between the Apgar scores at 1, 5, and 10 min; resuscitation measures; and umbilical artery blood analysis results of the two groups ($P > 0.05$) (Table 3).

Plasma Concentrations of Remifentanyl and Etomidate

No statistically significant differences were observed between the two groups in terms of the concentrations of remifentanyl in the MA, UA, and UV blood or the UA/UV and UV/MA ratios of remifentanyl immediately after umbilical cord ligation ($P > 0.05$) (Table 4). The plasma concentrations of etomidate in the MA and UV blood of group A at umbilical cord ligation were higher than those of group B, whereas the UA/UV ratios of etomidate concentration at umbilical cord ligation were higher in group B than those in group A ($P < 0.05$). No significant differences were observed between the two groups in terms of the concentrations of etomidate in UA blood and UV/MA ratio ($P > 0.05$) (Table 5).

Correlation analysis did not reveal a significant correlation between the I-D time and plasma remifentanyl concentrations in MA, UA, and UV. However, the mean concentrations of etomidate in the MA and UV blood were negatively correlated with the I-D time ($P < 0.05$; Figures 1 and 2).

Discussion

The negative impact of general anesthetics used to induce general anesthesia during CS on the fetus is a major source of concern. The fetal side effects are thought to be more severe due to the prolonged use of anesthetics for various reasons.

Table 1 General Information and Preoperative Laboratory Test Results of Two Groups

Parameters	All (n=52)	Group A (n=41)	Group B (n=11)	P value
Age (years)	31.79±2.67	31.74±4.25	32.00±3.89	0.860
Body weight (kg)	70.26±11.20	68.84±11.09	76.25±10.06	0.058
Height (cm)	157.92±5.17	157.43±5.16	160.00±4.94	0.160
BMI	28.13±4.09	27.73±4.07	29.82±3.94	0.149
Gestation (weeks)	38.76±0.86	38.84±0.87	38.42±0.77	0.160
GH (Yes/No)	4/48	3/38	1/10	0.845
GDM (Yes/No)	9/43	7/34	2/9	0.619
Previous CS (Yes/No)	18/34	12/29	6/5	0.118
Hemoglobin (g/L)	123.69±12.78	123.50±13.13	124.50±11.80	0.826
Hematocrit (%)	35.87±4.22	35.73±4.47	36.45±3.09	0.633
Leukocyte (× 10 ⁹ /L)	8.37±2.00	8.42±2.03	8.15±1.96	0.707
Platelet (× 10 ⁹ /L)	149.02±61.75	149.40±62.34	147.40±62.46	0.928
PT (s)	10.27±1.24	10.12±0.86	10.90±2.18	0.073
APTT (s)	26.12±1.81	26.04±1.69	26.44±2.31	0.537
FIB (g/L)	4.59±0.85	4.61±0.93	4.51±0.44	0.749
TT (s)	17.33±1.31	17.29±1.38	17.50±0.97	0.646
D-Dimer (mg/L) FEU	2.38±1.39	2.36±1.20	2.45±2.10	0.858
I-S (min)	2.67±0.63	2.65±0.64	2.86±0.55	0.349
I-D (min)	6.35±2.67	5.43±1.30	10.23±3.46	0.001*
U-D (second)	58.77±26.66	51.52±13.52	89.20±43.81	0.024*

Note: *Compared with Group A, $P < 0.05$.

Abbreviations: BMI, Body mass index; GDM, Gestational diabetes mellitus; GH, Gestational hypertension; CS, Cesarean section; PT, Plasma prothrombin time; APTT, Activated partial thrombin time; FIB, Plasma fibrinogen; TT, Thrombin time; I-S, induction-to-skin incision intervals; I-D, anesthesia induction to delivery intervals; U-D, uterine incision to delivery intervals.

Table 2 Reasons for Choosing General Anesthesia

Reasons	Number of Cases	Percentage
Emergency surgery for placental abruption	5	9.62%
Emergency surgery caused by fetal distress	1	1.92%
Thrombocytopenia	16	30.77%
Anticoagulant drugs were not stopped	5	9.62%
Abnormal coagulation function (Non-platelet factor)	1	1.92%
History of lumbar disc herniation or lumbar surgery	23	44.23%
Maternal requirements	1	1.92%

The negative impact of anesthetic drugs on the fetus is related to the rate of placental drug transport and the metabolism rate, which influence the concentration of drugs reaching the fetus.

The type of anesthesia used during CS is an important determinant of maternal and fetal outcomes.¹² All drugs administered to the mother during the induction of anesthesia cross the placenta in time and affect neonatal outcomes, such as respiratory and heart rate and muscular tension. Unstable maternal blood pressure, heart rate, uterine tone, and uteroplacental perfusion induced by any medication, including anesthetics, indirectly influence fetal performance. The I–D and U–D times are reliable prognostic factors for neonatal outcomes. The I–D and U–D times should not exceed 10 min and 3 min, respectively.¹

In an effort to determine the effect of I–D time on the fetal plasma concentration of remifentanyl at delivery, this study aimed to determine the extent of placental transport of remifentanyl and etomidate during CS under general anesthesia. Liquid chromatography-tandem mass spectrometry analysis revealed no correlation between the I–D time and fetal plasma concentrations of remifentanyl and etomidate.

Table 3 Neonatal Scores, Umbilical Artery Blood Gas Analysis and Resuscitation Measures of Two Groups

Parameters	All (n=52)	Group A (n=41)	Group B (n=11)	P value
Apgar scores at 1 min				0.350
10	37	31	6	
8-9	11	7	4	
4-7	4	3	1	
Apgar scores at 5 min				0.859
10	47	37	10	
8-9	4	3	1	
4-7	1	1	0	
Apgar scores at 10 min				0.308
10	50	40	10	
8-9	2	1	1	
Resuscitation measures				
Tactile stimulation	52	41	11	/
Bag-mask ventilation	7	6	1	0.632
Tracheal intubation	1	1	0	0.788
Umbilical artery blood				
pH	7.27±0.05	7.27±0.06	7.26±0.05	0.567
PaO ₂ (mmHg)	31.21±12.79	30.88±12.18	32.74±16.32	0.732
PaCO ₂ (mmHg)	55.41±8.14	55.37±7.93	55.63±9.73	0.939
Base excess (mmol/L)	-2.38±2.51	-2.26±2.61	-2.91±2.07	0.540

Table 4 Blood Concentrations of Remifentanyl of the Totality and Two Groups

Parameters	All (n=52)	Group A (n=41)	Group B (n=11)	P value
MA (ng/mL)	4.07±1.47	4.17±1.54	3.71±1.11	0.387
UV (ng/mL)	1.98±0.91	2.06±0.94	1.69±0.74	0.254
UA (ng/mL)	1.04±0.73	1.14±0.73	0.67±0.61	0.071
UV/MA ratio	0.49±0.16	0.50±0.16	0.46±0.15	0.465
UA/UV ratio	0.50±0.23	0.52±0.23	0.40±0.24	0.160

Table 5 Blood Concentrations of Etomidate of the Totality and Two Groups

Parameters	All (n=52)	Group A (n=41)	Group B (n=11)	P value
MA (ng/mL)	428.27±153.82	455.48±143.07	324.88±156.22	0.015*
UV (ng/mL)	304.35±130.11	331.81±128.31	199.99±73.66	0.003*
UA (ng/mL)	180.48±83.01	190.20±87.07	143.53±53.83	0.115
UV/MA ratio	0.72±0.18	0.73±0.18	0.68±0.21	0.366
UA/UV ratio	0.62±0.19	0.60±0.21	0.72±0.08	0.007*

Note: *Compared with Group A, P<0.05.

Based on previous literature⁶ and our practice data, the participants were divided into relatively shorter and longer groups according to I-D time. The I-D time was 5.43 and 10.23 minutes in the shorter and longer groups, respectively. This grouping method is sufficient to explain the impact of the prolonged I-D time and is consistent with clinical practice.

According to the 2019 obstetric anesthesia and analgesia Practice Guide of the American College of Obstetricians and Gynecologists,¹³ the choice of anesthesia should fully consider the urgency of the operation, contraindications of intraspinal puncture, and other factors. The proportion of CS performed under general anesthesia is 5.8% generally,

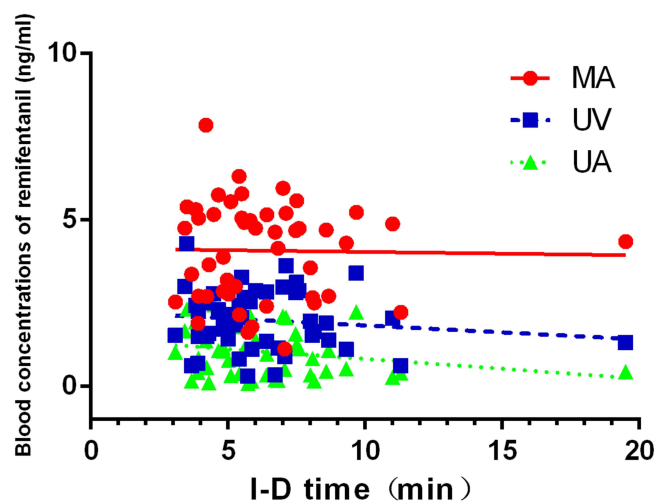


Figure 1 Correlation analysis of remifentanyl concentrations from maternal and neonatal blood (UV, UA) with I-D time. $r(\text{MA}) = -0.019$, $P = 0.897$; $r(\text{UV}) = -0.128$, $P = 0.386$; $r(\text{UA}) = -0.224$, $P = 0.125$.

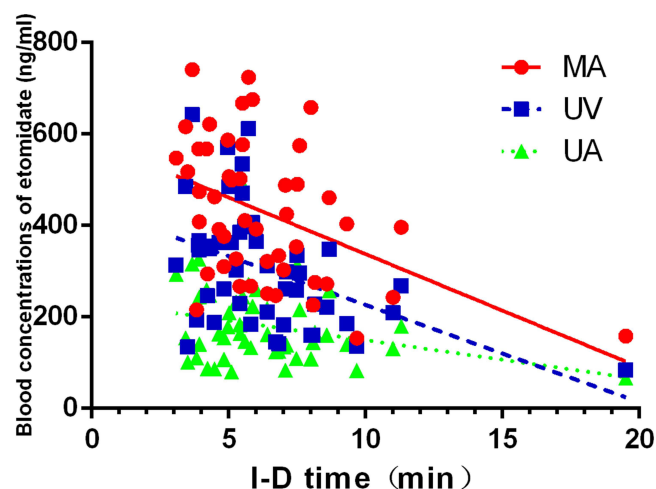


Figure 2 Correlation analysis of etomidate concentrations from maternal and neonatal blood (UV, UA) with I-D time. $r(\text{MA}) = -0.444$, $P = 0.002$; $r(\text{UV}) = -0.451$, $P = 0.001$; $r(\text{UA}) = -0.283$, $P = 0.051$.

which increases to 14.6% in the case of urgent CS.¹⁴ The data from our institute showed that general anesthesia was induced in 11.54% of cases due to emergent factors, of which 86.54% was due to contraindications for intraspinal puncture.

Remifentanyl is the optimal option if CS must be performed under general anesthesia, as it is an ultra-short-acting potent μ -receptor agonist with a context-sensitive half-time of 3–5 min. Placental transport occurs quickly, and the drug is metabolized and redistributed rapidly in the fetus when administered via intravenous infusion.⁵ Continuous intravenous infusion of low-dose remifentanyl at $0.05 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ could significantly improve the experience of parturients undergoing repeated CS under epidural anesthesia, without obvious maternal or neonatal adverse effects.¹⁵ Pre-delivery infusion of remifentanyl (0.06 – $0.46 \text{ mcg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) has no significant influence on airway interventions at birth or the neonatal Apgar scores at 1 and 5 min.⁴ Another study also reported that remifentanyl bolus ($1 \mu\text{g}\cdot\text{kg}^{-1}$) administered immediately before general anesthesia induction, followed by infusion at $0.15 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for elective CS significantly attenuated the maternal hemodynamic response and lipid peroxidation during the entire duration of I-D without compromising the neonatal outcomes.¹⁶ A meta-analysis, which included 17 studies ($n=987$), indicated the safety of

remifentanyl (0.5–1 $\mu\text{g}/\text{kg}$ or 2–3 $\mu\text{g}/\text{kg}/\text{h}$), with no significant side effects on the Apgar scores or neonatal respiratory intervention.¹⁷

In our study, Apgar scores of less than 8 accounted for 7.7% of the 52 neonates, and the prolonged I-D time had no effect on neonatal performance. Another study reported that the continuous intravenous infusion of propofol in combination with remifentanyl after the bolus dose for the induction of anesthesia during CS and prolongation of the I-D time (18 min) within a certain limit, had no adverse influence on the fetus.⁶ However, higher neonatal resuscitation needs (tactile stimulation 31.5% and bag-mask ventilation 50%) at 1 min were reported in a study when remifentanyl was administered at a loading dose of 2 $\mu\text{g}/\text{kg}$ over 10 min followed by a continuous infusion of 2 $\mu\text{g}/\text{kg}/\text{h}$,¹⁸ which is a different administering regimen from that used in our study. The differences between the enrolled participants and the remifentanyl administration protocol also influenced the outcomes, indicating that closed monitoring and resuscitation preparation are important in clinical practice.

The two groups showed no differences in terms of the remifentanyl concentrations in the MA, UA, and UV plasma or the UA/UV and UV/MA ratios of remifentanyl concentration immediately after umbilical cord ligation, indicating that the I-D time did not affect the amount of remifentanyl transported to the fetus. No correlation was observed between the blood remifentanyl concentrations (MA, UV, and UA blood) and I-D time. A previous study reported that the mean concentrations of remifentanyl in the MA, UA, and UV blood at delivery in the shorter time (I-D) group were 2.25, 1.43, and 0.65 ng/mL , respectively, whereas those in the longer time (I-D) group were 1.96, 1.25, and 0.75 ng/mL respectively.⁶ However, the I-D interval grouping cut-off was 16 min in this previous study (depending on the time of disinfection and surgical towel placement), whereas it was 8 min in our study. In addition, the remifentanyl administration methods (1 $\mu\text{g}/\text{kg}$ for induction and 7 $\mu\text{g}/\text{kg}/\text{h}$ for maintenance) also differed from those used in our study (TCI of remifentanyl 5 ng/mL , TCI). Kan et al⁵ reported that the mean UV/MA and UA/UV ratios of remifentanyl were 0.88 ± 0.78 and 0.29 ± 0.07 when remifentanyl was infused intravenously at $0.1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The interaction between the combination of drugs and different detection methods (compared with gas chromatography with high-resolution mass spectrometry-selected ion monitoring, liquid chromatography-tandem mass spectrometry analysis has a strong separation ability and lower detection limit) may have caused the deviation between the studies.

The placental transport rate of etomidate is higher than that of remifentanyl. The plasma etomidate concentrations in the MA and UV blood were reduced due to single administration when the I-D time was prolonged. The etomidate concentrations in the MA and UV plasma were negatively correlated with the I-D interval. This kind of negative correlation was not observed in UA. This may be because UA blood is the end of drug metabolism and etomidate is given as a single dose in the study.

A combination of intravenous and inhalation anesthesia was selected to achieve sufficient anesthesia depth in a short time and avoid intraoperative awareness, and sevoflurane was used in the induction phase but was stopped immediately after intubation to avoid its effects on uterine contraction. Pre-exposure to low concentrations of sevoflurane reduced the bispectral index values in the interval before delivery, indicating that this method may reduce the risk of maternal intraoperative awareness.¹⁹

Our study has some limitations. Since collecting neonatal blood was difficult, the drug metabolism in the neonatal blood could not be measured continuously. Moreover, drug transport during general anesthesia in preterm births and twins requires further study.

In conclusion, remifentanyl, in combination with etomidate and sevoflurane by TCI, can be used safely for the induction of general anesthesia during CS. A prolonged I-D time (8 min) did not influence the plasma remifentanyl concentration in neonates or result in any neonatal side effects.

Data Sharing Statement

The data presented in this study are available on request from the corresponding author (Jin Yu; dodoes@qq.com). The data are not publicly available because this is a clinical trial containing information that could compromise the privacy of research participants.

Ethics Approval and Consent to Participate

This trial was approved by the Medical Ethics Committee of Chongqing Health Center for Women and Children (reference number: 2021-011) and registered with Chinese Clinical Trial Registry (ChiCTR) (www.chictr.org.cn, registration number: ChiCTR2100046547). The trial was performed in accordance with International Conference on Harmonization - Guidelines for Good Clinical Practice (ICH-GCP) and Declaration of Helsinki. Informed consents were obtained from all participants.

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Author Contributions

JY designed the study. XL and JM coordinated the clinic procedures and laboratory tests. MC, HL and YP conducted the drug concentration tests. JY and MC performed the statistical analyses and drafted the paper. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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