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A pilot study on LC–MS/MS quantification of remifentanil, etomidate, and rocuronium in maternal and fetal serum microsamples

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While remifentanil, etomidate, and rocuronium are increasingly used for cesarean section due to their favorable hemodynamic stability and fetal safety profile, their pharmacokinetics and potential effects on neonates remain poorly understood. This study developed and validated a rapid, sensitive LC–MS/MS method for simultaneous quantification of the three anesthetics in microsamples of 10 µl serum, followed by a paired maternal and umbilical cord serum investigation. After protein precipitation with acetonitrile, analytes were separated within 4 min using positive electrospray ionization in MRM mode. Method validation demonstrated excellent linearity ($R^2 > 0.99$) for all compounds, with LLOQs of 0.15 ± 0.02 ng/mL (remifentanil), 16.87 ± 0.51 ng/mL (etomidate), and 106.73 ± 8.63 ng/mL (rocuronium). Precision (intra-/inter-day < 15%) and minimal carry-over (< 5%) met bioanalytical standards. Applied to 20 maternal-newborn pairs, the method quantified differential drug distribution: maternal arterial concentrations (remifentanil 4.75 ± 0.19 ng/mL; etomidate 412.71 ± 35.29 ng/mL; rocuronium 7.08 ± 0.48 µg/mL) exceeded umbilical vein levels (2.43 ± 0.13 ng/mL; 302.15 ± 29.03 ng/mL; 0.86 ± 0.16 µg/mL), which were higher than umbilical artery concentrations (1.33 ± 0.15 ng/mL; 166.24 ± 21.53 ng/mL; 0.44 ± 0.77 µg/mL). Calculated placental transfer rates significantly differed among anesthetics (remifentanil 0.52 ± 0.02; etomidate 0.75 ± 0.04; rocuronium 0.13 ± 0.02; all $P < 0.001$), reflecting distinct pharmacokinetic behaviors. The validated method enables reliable microvolume analysis for perinatal pharmacokinetic studies, particularly valuable when sample availability is limited. Its rapid throughput and sensitivity make it suitable for clinical research applications investigating maternal–fetal drug transfer dynamics.

Keywords Anesthetics, Caesarean section, LC–MS/MS, Newborn

Recently, induction of anesthesia using propofol, rocuronium, and remifentanil are becoming popular[1]. Compared with propofol, etomidate has minimal impact to hemodynamics with low fluctuation of blood pressure and cardiac rhythm[2]. Therefore, the three anesthetics remifentanil, etomidate, and rocuronium are another choice for cesarean section, especially for pregnant women who have cardiovascular problems[3–5]. The three drugs operate through complementary mechanisms: remifentanil is an opioid analgesic; etomidate, a general anesthetic; and rocuronium, a muscle relaxant. Remifentanil is the preferred opioid analgesic for this situation: although it easily passes through the placental barrier, it is hydrolyzed in cord blood and rapidly metabolized in the fetus, and it is less likely to cause respiratory depression[6]. Etomidate and rocuronium are assumed to present minimal risk to fetal breathing because they are both administered at single dose[7,8]. However, the effect of the triple combination on fetal respiration has not been systematically analyzed, nor are the pharmacokinetics of the drugs in the mother and newborn well understood, which means their long-term safety is unclear.

Pharmacokinetic and safety studies require appropriate analytical methods for determining all three anesthetics in blood, yet published methods whether based on high-performance liquid chromatography or

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liquid chromatography-tandem mass spectrometry require large sample volumes and time- or labor-intensive procedures and have been validated for only one or two of the three drugs[3,4]. Therefore, we undertook the present study to develop and validate a single analytical method that could accurately determine all three anesthetics in extremely small volumes of serum. As a methodological application, we performed a pilot study using matched maternal-cord blood pairs to investigate transplacental drug transfer dynamics and maternal–fetal concentration gradients.

Results

The outcomes present both method development/validation data and its successful application in paired maternal-neonatal serum specimens, outlined in Fig. 1.

Column chromatography lasting 4 min was sufficient to cleanly separate the three anesthetics of interest from their respective internal standards (Fig. 2). Retention time did not vary significantly when samples were analyzed on different days (data not shown). The method showed good linear response for all three anesthetics (Table 1), and LLOQs were 0.08 ± 0.01 ng/ml for remifentanil, 18.69 ± 0.14 ng/ml for etomidate, and 106.73 ± 8.63 ng/ml for rocuronium (Table 2). For all three anesthetics, intra- and inter-day imprecision was below 15% (Table 3), recovery was 85–115% (Table 4), and carry-over was below 15% (Table 5).

These results indicate that our analytical method is valid. Using this method, we determined levels of the three anesthetics in maternal arterial blood and in the blood from umbilical veins and arteries (Table 6). The mean concentration of remifentanil in maternal arterial blood was 4.75 ng/ml, in good agreement with the target-controlled infusion concentration of 5 ng/ml during anesthesia induction. The ratios of drug concentration in umbilical veins to the concentration in maternal arteries, which reflect rate of transport from mother to fetus, were 0.52 ± 0.02 for remifentanil, 0.75 ± 0.04 for etomidate, and 0.13 ± 0.02 for rocuronium ($P < 0.001$).

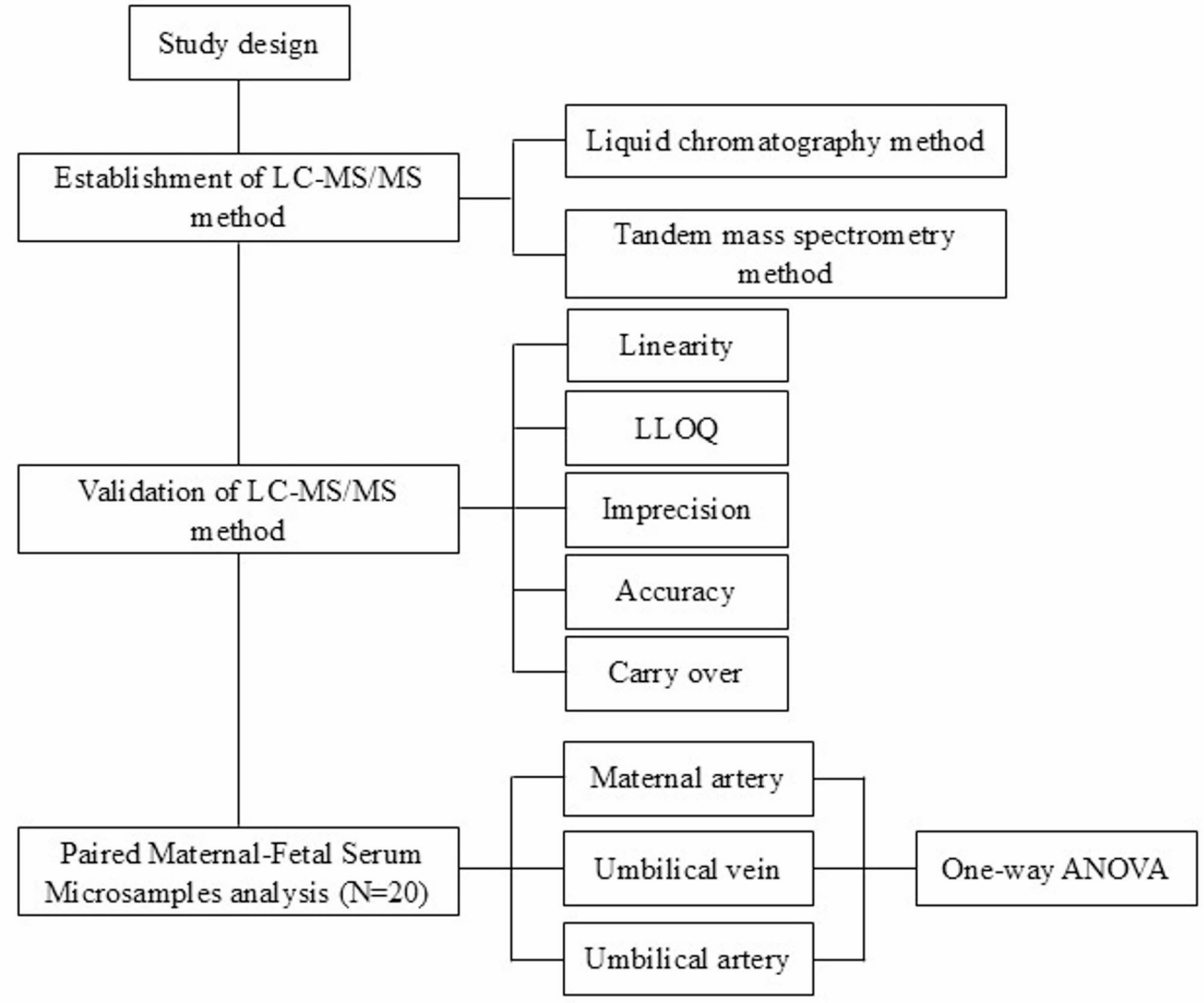

Fig. 1. Study workflow overview.

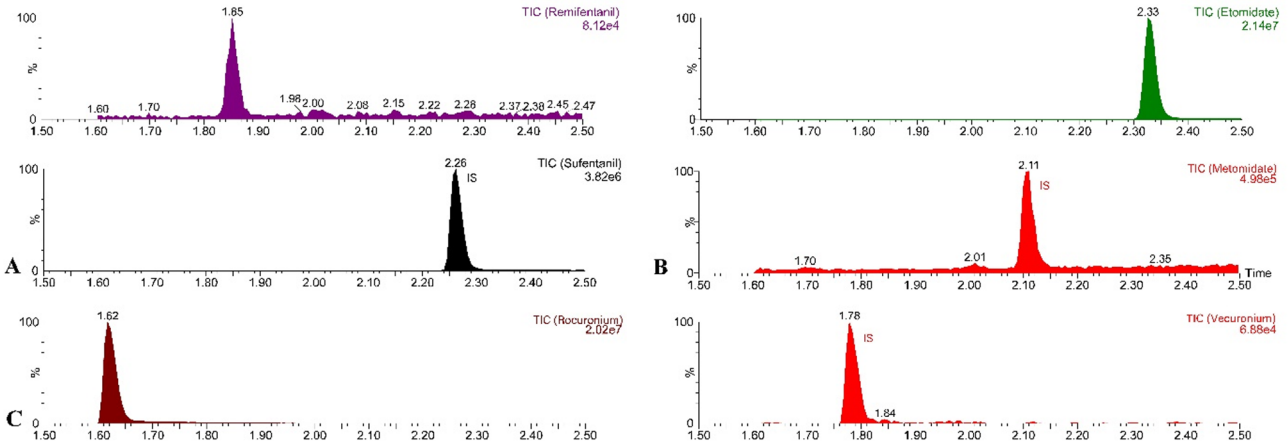

Fig. 2. Representative total ion chromatograms (TICs) of (**A**) remifentanil and its internal standard sufentanil, (**B**) etomidate and its standard metomidate, or (**C**) rocuronium and its standard vecuronium. In all chromatograms, the x-axis shows the retention time (min), while the y-axis shows relative ion intensity. The exact ion intensity is indicated at the upper right of each chromatogram.

Analyte	Regression equation	R^2
Remifentanil	$Y = 0.997044X + 0.0197252$	0.994
Etomidate	$Y = 0.181642X + 0.181636$	0.997
Rocuronium	$Y = 0.00873526X + 1.30879$	0.992

Table 1. Linear regression of calibration curves for the three anesthetics.

Analyte	LLOQ (ng/ml)	Relative standard deviation (%)	Signal/noise ratio
Remifentanil	0.15 ± 0.02	16.08	≥ 10
Etomidate	16.87 ± 0.51	3.01	≥ 10
Rocuronium	106.73 ± 8.63	8.09	≥ 10

Table 2. Lower limits of quantification (LLOQ) for the three anesthetics * Values are mean ± SD, unless otherwise noted. * From three replicates in one experiment.

Analyte	Level	Intra-day*		Inter-day**	
		Concentration (ng/ml)	RSD (%)	Concentration (ng/ml)	RSD (%)
Remifentanil	Low	0.54 ± 0.08	15.41	0.52 ± 0.03	4.63
	Interm	1.49 ± 0.19	12.77	2.14 ± 0.24	11.05
	High	2.55 ± 0.31	12.30	4.11 ± 0.55	13.31
Etomidate	Low	95.25 ± 8.86	9.30	110.12 ± 4.02	3.65
	Interm	405.63 ± 46.03	11.35	520.48 ± 31.75	6.10
	High	783.55 ± 75.60	9.65	969.65 ± 126.89	13.09
Rocuronium	Low	1102.59 ± 134.60	12.21	1174.87 ± 122.67	10.44
	Interm	2937.89 ± 332.78	11.33	4342.86 ± 473.68	10.91
	High	4487.83 ± 450.81	10.05	8188.54 ± 408.94	4.99

Table 3. Intra- and inter-day imprecision in determination of the three anesthetics. Values are mean ± SD, unless otherwise noted. Interm, intermediate; RSD, relative standard deviation. * From 20 replicates of each concentration within the same day. **From five measurements made once daily on five consecutive days.

Analyte	Level	Concentration (ng/ml)		RSD (%)	Recovery (%)
		Nominal	Measured*		
Remifentanil	Low	0.50	0.53 ± 0.04	7.55	106.00
	Interm	2.00	2.27 ± 0.17	7.49	113.50
	High	4.00	4.38 ± 0.47	10.73	109.50
Etomidate	Low	125.00	127.45 ± 10.04	7.88	101.96
	Interm	500.00	518.81 ± 28.94	5.58	103.76
	High	1000.00	1143.26 ± 115.00	14.48	114.33
Rocuronium	Low	1000.00	1096.43 ± 118.21	10.78	109.64
	Interm	4000.00	4160.96 ± 261.63	6.29	104.02
	High	8000.00	7430.55 ± 816.68	10.99	92.88

Table 4. Accuracy of determination of the three anesthetics. Values are mean ± SD, unless otherwise noted. Interm, intermediate. * From five measurements made once daily on five consecutive days.

Analyte	Sample (See methods)			Residual (%)
	High3	Low1	Low3	
Remifentanil	9.62	0.00	0.16	− 1.66
Etomidate	1758.00	46.98	37.87	− 0.53
Rocuronium	14,731.36	627.60	611.86	− 0.11

Table 5. Carry-over during determination of the three anesthetics. Values are concentrations in ng/ml, unless otherwise noted.

Serum source	(1)Maternal artery	(2)Umbilical vein	(3)Umbilical artery	Ratio (2)/(1)
Remifentanil (ng/ml)				
Mean ± SD	4.75 ± 0.19	2.43 ± 0.13	1.33 ± 0.15	0.52 ± 0.02
Range	2.77 ~ 5.79	1.32 ~ 3.39	0.31 ~ 2.44	0.30 ~ 0.65
Etomidate (ng/ml)				
Mean ± SD	412.71 ± 35.29	302.15 ± 29.03	166.24 ± 21.53	0.75 ± 0.04
Range	153.65 ~ 667.81	83.91 ~ 534.32	66.31 ~ 490.44	0.24 ~ 0.97
Rocuronium (μg/ml)				
Mean ± SD	7.08 ± 0.48	0.86 ± 0.16	0.44 ± 0.77	0.13 ± 0.02
Range	2.44 ~ 12.30	0.29 ~ 3.73	0.19 ~ 1.44	0.03 ~ 0.47
P	ND	ND	ND	< 0.001

Table 6. Concentrations of the three anesthetics in different sources of serum and their ratios * * From 20 maternal–fetal pairs. ND, not done.

Discussion

Here we describe and validate an analytical method to simultaneously determine three anesthetics commonly given to pregnant women during cesarean section deliveries in maternal as well as umbilical blood. The method requires very small amounts of serum, which undergoes a straightforward protein precipitation procedure, followed by liquid chromatography and tandem mass spectrometry. With a measurement duration of under 4 min (faster than prior reports), the method offers significantly improved efficiency, making it particularly suitable for research involving large sample sizes[9,10]. Besides, this method also shows satisfactory LLOQs, linearity, precision and accuracy for determining remifentanil, etomidate and rocuronium.

Our protein precipitation approach is similar to that reported in other methods designed to analyze individual anesthetics in our study, but not all of them together[11,12]. The protein precipitation procedure in our method provides good sensitivity, with LLOQs as low as 0.08 ng/ml, even though it uses only 10 μl of serum for analysis. This gives our relatively straightforward method a strong advantage over other approaches that require more complicated processing, such as solid-phase extraction or microextraction in a packed syringe[13,14]. Our LLOQ for remifentanil is higher than that of another method involving liquid–liquid extraction (0.08 vs. 0.05 ng/ml), yet that method requires approximately 500 μl of serum[15].

Rocuronium was nearly 4000 times more concentrated in maternal and umbilical serum than remifentanil or etomidate, which poses a challenge for their simultaneous determination. The success of our method depends on a suitably sensitive tandem mass spectrometry system that can accurately determine ions present

at concentrations spanning five orders of magnitude[16]. We had to carefully optimize sample concentration and injection volume to prevent oversaturation by rocuronium.

Applying this method to a small sample of women giving birth by cesarean section at our hospital, we achieved precise quantification of drug concentrations at both nanogram (ng) and microgram (μg) levels, demonstrating the high sensitivity. More notably, we found rates of anesthetic transfer from mother to newborn varied significantly widely. These rates likely depend on several drug characteristics, such as size, lipophilicity, affinity for transporter proteins and extent of ionization[17]. The low transfer of rocuronium reflects its high water-solubility, which inhibits its passage through the placental barrier[18]. While rocuronium exhibits a significantly lower transfer rate compared to remifentanil and etomidate, its association with decreased 1-min Apgar scores (though 5-min scores remain largely unaffected) raises important clinical concerns[19]. Remifentanil is known to be distributed and metabolized faster in the newborn than in the mother because of newborns' higher concentration of red blood cells in the circulation and their lower proportion of subcutaneous fat[20]. Whether the same is true for the other two anesthetics remains to be seen. In contrast to the different rates of transfer, rates of metabolism in the newborn were between 0.50 and 0.60 for all three anesthetics. Previous work reported a much higher rate of remifentanil transport from mother to newborn of 0.88 when the drug was used on its own, but only a slightly higher rate of 0.64 when it was used with propofol[21,22]. Combining remifentanil with propofol or etomidate may decrease its transport from mother to newborn, which should be explored in future research.

Our method should facilitate detailed studies of the pharmacokinetics of these drugs in the mother and newborn in order to verify their safety and identify any additive or antagonistic interactions among them. Still, the current study has several limitations worth noting: (1) the small cohort size may affect extrapolation of our pharmacokinetic observations to broader populations, and (2) restriction to single time-point measurements precludes evaluation of temporal metabolic patterns that could influence drug transfer ratios.

Methods

Study design

The study had two objectives: first, to develop and validate a sensitive LC–MS/MS assay for simultaneous measurement of remifentanil, etomidate, and rocuronium in serum; second, to implement this assay in paired maternal-neonatal serum analyses. Ethical approval was granted by the Ethics Committee of Chongqing Health Center for Women and Children (Approval No. 2021–011), and informed consent was obtained from all participating women. It was registered with the Chinese Clinical Trial Registry (registration ID: ChiCTR2100046547). All methods were performed in accordance with the relevant guidelines and regulations.

Reagents

HPLC-grade methanol and acetonitrile were purchased from Fisher Scientific (Geel, Belgium), and formic acid was purchased from Shanghai Aladdin Bio-Chem Technology (Shanghai, China). The following six narcotics were purchased from Toronto Research Chemicals (Toronto, Canada): remifentanil hydrochloride, sufentanil citrate, etomidate, metomidate hydrochloride, rocuronium bromide, and vecuronium bromide. Water in this study was purified using a Milli-Q apparatus (Millipore, Bedford, MA, USA).

Calibration standards, internal standards, and quality control samples

Stock solutions of remifentanil, etomidate, and rocuronium were prepared individually by dissolving solid compound into methanol to a concentration of 1 mg/ml, then vortexing at 1500 rpm for 5 min. The solutions were stored in brown vials at − 80 ℃ and used within 12 months. These stock solutions were combined and suitably diluted into serum from pregnant women unexposed to the three anesthetics to yield final concentrations of 10 ng/ml remifentanil, 20,000 ng/ml etomidate and 2000 ng/ml rocuronium. This working solution was stored in brown vials at − 20 °C and used within one month.

Stock solutions of the three internal standards sufentanil, metomidate and vecuronium were prepared individually by dissolving solid compound into acetonitrile to a concentration of 1 mg/ml, then vortexing at 1500 rpm for 5 min. These stock solutions were combined and suitably diluted into acetonitrile to yield final concentrations of 5 ng/ml sufentanil, 5 ng/ml metomidate, and 100 ng/ml vecuronium. This working solution was stored at − 20 °C in brown vials and used within one month.

Working solutions were diluted serially 1:2 in serum from pregnant women unexposed to the three anesthetics in order to determine calibration curves. Quality control samples were prepared by diluting working solutions into serum from unexposed pregnant women as follows: remifentanil, 0.5, 2.0 and 4.0 ng/ml; etomidate, 125.0, 500.0 and 1000.0 ng/ml; and rocuronium, 1000.00, 4000.00 and 8000.00 ng/ml.

Sample collection and preparation

Blood sample were taken from women giving birth by cesarean section under general anesthesia at our hospital. Blood for blank matrix was collected from pregnant women not yet exposed to anesthetics during venous access establishment. All women received anesthesia according to standard protocols at our hospital. General anesthesia was induced using target-controlled infusion of remifentanil (5 ng/ml), 5% sevoflurane inhalation, and intravenous etomidate (0.25 mg/kg), followed by intravenous rocuronium bromide (0.6 mg/kg). After rocuronium administration, the endotracheal tube was placed and connected to a ventilator. Sevoflurane was administered briefly and discontinued when the eyelash reflex disappeared. Immediately after ligation of the umbilical cord, blood was collected from the left radial artery of the mother as well as from the umbilical vein and artery. After umbilical cord ligation, anesthesia was maintained through target-controlled infusion of propofol at 3.5 μg/ml and of remifentanil at 5 ng/ml.

All the blood sample was centrifuged at 3000 rpm, and the serum was transferred to vials and stored at − 80 °C until analysis. Frozen samples were thawed at room temperature for about 20 min, and 10-μl volumes of

Analyte	Ion *m/z*		Retention time (min)	Cone energy (V)	Collision energy (V)
	Precursor	Product			
Anesthetics					
Remifentanil	377.0	113.2	1.85	6	30
		317.4		6	16
Etomidate	244.9	95.2	2.33	4	24
		141.2		4	8
Rocuronium	529.1	112.3	1.62	30	35
		487.5			
Internal standards					
Sufentanil	387.0	111.1	2.26	30	35
		238.3		6	18
Metomidate	230.9	95.17	2.11	2	24
		127.2		2	8
Vecuronium	557.8	100.5	1.78	30	35
		356.3		30	35

Table 7. Chromatographic retention times and mass spectrometric parameters of analytes in this study.

the thawed samples, quality control solutions and standards were placed into fresh microcentrifuge tubes, diluted up to 50 µl with pure water and vortexed at 1500 rpm for 3 min. Then 150 µl of acetonitrile containing internal standards was added to the vials, the solution was mixed and incubated at −20 °C for 20 min to precipitate proteins, and the solution was centrifuged at 13,000 g for 5 min at 4 °C. The supernatant (100 µl) was transferred into fresh microcentrifuge tubes.

An aliquot of supernatant (10 µl) was diluted with water (90 µl) to ensure accurate determination, and an aliquot of the dilution (3 µl) was injected into the liquid chromatography system for analysis as described below.

Liquid chromatography-tandem mass spectrometry

Samples were analyzed on an ultra-high performance liquid chromatography-tandem mass spectrometry system (Xevo TQ-S, Waters Corporation, Milford, MA, USA) equipped with an electrospray ionization source operating in positive mode. Samples were fractionated on a reverse-phase Acquity BEH C18 column (50 × 2.1 mm, 1.7 µm; Waters Corporation) under the following gradient of 0.1% (v/v) formic acid in water (solution A) and a 1:1 (v/v) mixture of methanol and acetonitrile in solution A (solution B): 0 to 0.6 min, 10% B; 0.6–2.8 min, 10–90% B; 2.8–3.6 min, 90% B; and 3.6–4 min, 10% B. The flow rate was 0.4 ml/min and column temperature was 45 °C.

Eluted compounds were analyzed in multiple reaction monitoring mode based on time-scheduled events with analyte-dependent parameters (Table 7) and the following additional parameters: ion source temperature, 150 °C; capillary voltage, 3.0 kV; desolvation temperature, 500 °C; gas flow rate for desolvation, 800 L/h; and gas flow rate in the cone, 150 L/h. Data were processed and quantified in MassLynx 4.2 software (Waters Corporation) based on the peak area and calibration with the internal standards. Amounts were quantified based on peak areas according to the internal standard method.

Validation of the analytical method

To assess linearity and the lower limit of quantitation (LLOQ), we prepared eight concentrations of each of the three anesthetics covering the following ranges: remifentanil, 0.08 to 10.00 ng/ml; etomidate, 15.63 to 2000 ng/ml; and rocuronium, 156.25 to 20,000 ng/ml. The ratio of each analyte's peak area to the peak area of its corresponding internal standard was plotted against the nominal spiked concentration. A calibration curve was generated using linear least-squares regression. The method was considered valid if the correlation coefficient (R^2) of the regression line exceeded 0.99.

The LLOQ was defined as the lowest concentration at which the signal-to-noise ratio was at least 10 and the coefficient of variation was below 20%. Accuracy was assessed in terms of the relationship between measured concentrations and nominal spiked concentrations in quality control samples. Imprecision was expressed as the relative standard deviation (RSD%) for quality control samples at low, intermediate and high concentrations. Twenty replicates of each concentration were determined within a single day (intra-day imprecision) or once daily on five consecutive days (inter-day imprecision). The method was considered valid if accuracy was 85–115% overall and 80–120% at the LLOQ, and if inter- and intra-day imprecision was below 15% overall and below 20% at the LLOQ.

Carry-over was assessed by analyzing three consecutive samples with high concentrations (H1, H2, H3) followed by three consecutive samples with low concentrations (L1, L2, L3). The carry-over rate was calculated as [(L1–L2) / (H3–L3)] × 100%. The method was considered valid if the carry-over rate was below 15% overall and below 20% at the LLOQ.

Statistical analysis

Data were reported as mean ± standard deviation, unless stated otherwise, as calculated in Microsoft Excel. Differences were assessed for significance using one-way ANOVA in SPSS 25 (IBM, Armonk, NY, USA).

Data availability
The data that support the findings of this study are available on request from the corresponding author.

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Author contributions
H L, raw data processing, manuscript writing and execution. M C, sample and clinical information collection. Y P: statistical analysis. JK M, table and figure preparation. J Y, manuscript revision and study design. The authors has accepted responsibility for the entire content of this manuscript and approved its submission.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
Blood sampling and analysis were approved by the Medical Ethics Committee of Chongqing Health Center for Women and Children (2021–011). The women provided informed consent for their blood and umbilical blood to be sampled and analyzed in this study.

Additional information
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