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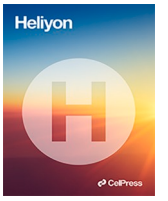

Research article

Exploring the Utility of remimazolam in cesarean sections under general anesthesia: A preliminary retrospective analysis and Implications for future study

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ABSTRACT

Background: Remimazolam has recently been introduced as a maintenance agent for general anesthesia. However, the effect of remimazolam on peripartum prognosis has not been reported. Therefore, this study aimed to compare the effects of remimazolam and propofol for uterotonic drugs following cesarean section.

Methods: The electronic medical records of 51 adult women who underwent elective cesarean sections by single obstetrician under general anesthesia were collected. Participants were categorized into two groups: the propofol group and the remimazolam group. General anesthesia was maintained by continuous infusion of propofol or remimazolam after delivery. The number of uterotonic drugs administered during the cesarean section, the estimated blood loss (EBL), and length of hospital stay (LOS) after delivery were assessed.

Results: Of the 51 patients included in the study, 35 were in the propofol group and 16 in the remimazolam group. In the remimazolam group, five patients (31.3%, 5/16) received more uterotonics than the standard regimen. Conversely, in the propofol group, 19 patients (54.3%, 19/35) were injected with more uterotonics than the standard regimen. Logistic regression analysis showed that abnormal positioning of the placenta ($P = 0.079$) and not using remimazolam ($P = 0.100$) were the most relevant factors associated with the increased use of uterotonics. There was no significant difference in EBL between the two groups. The use of remimazolam was clinically relevant with a shorter LOS ($P = 0.059$).

Conclusions: The use of remimazolam as a maintenance agent did not result in significantly higher use of intrapartum uterotonics compared to the use of propofol. These results cannot exclude all adverse effects of remimazolam during cesarean delivery. Further randomized controlled trials must be conducted to obtain high-quality evidence.

1. Introduction

Cesarean sections are performed to ensure the safety of both the mother and fetus and various anesthesia methods have been utilized for this purpose. During cesarean delivery under general anesthesia, anesthesia induction typically involves the use of propofol

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or thiopental and is maintained by either a combination of low-dose inhalational anesthetic agent and nitrous oxide or through the administration of sedatives [1].

Remimazolam, a recently introduced sedative, has gained attention as a safer alternative and has shown potential as a maintenance agent for general anesthesia [2]. In a phase 3 clinical trial comparing total intravenous anesthesia using remimazolam and propofol in patients under general anesthesia, no significant differences in time to loss of consciousness, extubation time, or occurrence of adverse events were found [3]. Moreover, postoperative nausea and vomiting after laparoscopic surgery were significantly reduced in patients treated with remimazolam compared to those treated with desflurane [4]. Since its introduction, remimazolam has been used in various surgeries requiring sedation and general anesthesia. It has the advantage of maintaining sedation without respiratory depression [5], and its sedative effects can be effectively reversed by the antagonist flumazenil when an overdose is suspected. Therefore, anesthesiologists in our hospital have adopted the practice of continuously administrating remimazolam to mothers following delivery to sustain anesthesia.

The selection of an anesthetic agent for cesarean sections is determined by assessing its effects on uterine contractions and the prognosis of the baby after delivery. For example, a high concentration of inhaled anesthetic can result in insufficient uterine contractility [6]. While in-vitro studies have suggested that propofol tends to relax the smooth muscles of the uterus in pregnant women [7], clinical evidence supporting this claim is still lacking. However, studies utilizing remimazolam under general anesthesia for cesarean sections have not yet been reported. The absence of in vitro studies on the uterine muscles or clinical studies involving mothers raises concerns regarding the use of remimazolam for cesarean sections. Therefore, it is imperative to collect clinical data and elucidate the relationship between uterine contractions and the administration of remimazolam before considering the introduction of this new anesthetic agent for cesarean sections.

This retrospective study aimed to compare the clinical outcomes between mothers who received general anesthesia with propofol and those who received general anesthesia with remimazolam during cesarean sections. The primary outcome of this study was insufficient uterine contractions. To quantify uterine contractions, we analyzed the number of uterotonic drugs administered to patients as the primary outcome. Additionally, intraoperative estimated blood loss (EBL), the incidence of postpartum hemorrhage (PPH), and length of hospital stay (LOS) were analyzed. Indications of reduced use of uterotonic drugs administered during cesarean section with remimazolam compared to propofol may warrant further investeigation through prospective studies on this topic.

2. Methods

This retrospective data analysis study was conducted at a single tertiary hospital and received approval from the Institutional Review Board of Korea University Anam Hospital (IRB No. 2022AN0439). The requirement to obtain informed consent was waived as all data were collected retrospectively. Data from adult pregnant women aged 19 years or older who underwent cesarean sections under general anesthesia performed by a single obstetrician at Korea University Anam Hospital between April 1, 2021 and August 31, 2022 were included. Only patients who received a continuous infusion of either propofol or remimazolam for maintenance agent under general anesthesia after delivery were included. Patients who received both propofol and remimazolam and those with insufficient data were excluded from the study.

The primary outcome was the number of uterotonics administered by the attending obstetrician during cesarean sections. “More use of uterotonics” (MU) was defined as the administration of three or more types of uterotonics (oxytocin 20 IU, carbetocin 100 μg, methylergometrine 0.2 mg, or sulprostone 1000 μg) during delivery. Cases where two or fewer drugs were administered were categorized as “Lesser use of uterotonics” (FU). Because this study was retrospective, there were limitations in collecting accurate data. Although it would have been ideal to determine the exact amount of blood loss as the primary outcome, this was not feasible. In the case of anesthesiologists, EBL was evaluated based on the volume of suction bottles and the number of gauzes use [8], but there may have been variations depending on the skill level of anesthesiologists. Additionally, the obstetrician recorded blood loss as either more than or less than 300 mL. This metric was recorded immediately after surgery by the obstetrician, who had been present with the patient from the onset of the surgical procedure and had accurately measured the amount of pure blood, excluding amniotic fluid. Therefore, the type and amount of uterotonic medication prescribed was the most accurate record.

Secondary outcomes included the EBL during surgery, the incidence of PPH, and postoperative LOS. All cesarean sections included in this study were performed by a single obstetrician. The obstetrician kept the patient who underwent a cesarean section in the hospital for 5 days postoperatively. The patients were cleared for discharge on postoperative day 5 after the gauze pad was free of blood and the staples from the surgical incision have been removed. Therefore, the postoperative LOS was also collected as a secondary outcome measure because it was related to bleeding.

To determine the sample size, medical records of mothers who underwent elective cesarean sections under general anesthesia between January and April 2022 were collected. The control group comprised nine patients who received propofol infusion to maintain anesthesia (propofol group), while the experimental group comprised seven patients who received remimazolam infusion (remimazolam group). Among the propofol group, 66.7% belonged to MU, while 14.3% of the remimazolam group was MU. With a power level of 90%, a significance level of 0.05 and allocation ratio 2:1, a total of 37 patients (12 patients in remimazolam group and 25 patients in propofol group) were planned to be collected in the study.

The standard anesthesia procedure for cesarean sections in this hospital was as follows: upon entering the operating room, the mother received 100% oxygen for at least 3 min. Loss of consciousness was induced using thiopental (4 mg/kg of actual body weight). Neuromuscular blockade was induced using succinylcholine (1 g/kg of prepartum body weight). After muscle fasciculation and relaxation were observed, intubation was performed using an endotracheal tube that was one unit smaller than the usual size. Capnography was then conducted to confirm airway patency. A mixture of sevoflurane, oxygen, and nitrous oxide was administered until

delivery to keep the bispectral index (BIS) below 60. After clamping the umbilical cord, all mothers received 20 IU oxytocin mixed with 1 L of isotonic balanced crystalloid (Plasma Solution-A injection, HK inno. N, South Korea). Inhalation anesthesia was discontinued, and either propofol (Fresofol MCT 2%, Fresenius Kabi, Singapore) or remimazolam (Byfavo, Hana Pharmaceuticals, South Korea) was administered for maintenance to keep the BIS consistently below 60. Additionally, fentanyl was administered for pain relief.

The attending obstetrician, who was blinded to the group allocation, assessed the status of the mother's uterine contractions and

Table 1
Demographic and clinical characteristics of the patients included in this study.

	All patients (n = 51)		Remimazolam group (n = 16)		Propofol group (n = 35)		*P*-value
Demographic data							
Age (years)	34.0	±4.4	33.9	±3.6	34.0	±4.8	0.927
BMI, preoperative (kg/m^2)	22.5	±3.8	24.2	±4.4	21.8	±3.3	0.038
Comorbidities							
Hypertension	1	(2.0)	1	(6.3)	0	(0.0)	0.135
Heart failure	0	(0.0)	0	(0.0)	0	(0.0)	(−)
COPD	0	(0.0)	0	(0.0)	0	(0.0)	(−)
Cerebrovascular diseases	0	(0.0)	0	(0.0)	0	(0.0)	(−)
Diabetes mellitus	12	(23.5)	4	(25.0)	8	(22.9)	0.867
Chronic renal diseases	0	(0.0)	0	(0.0)	0	(0.0)	(−)
Metastatic cancer	1	(2.0)	1	(6.3)	0	(0.0)	0.135
Intraoperative data							
Reason for cesarean section:							
Previous history of cesarean section	20	(39.2)	9	(56.3)	11	(31.4)	0.092
Oligohydramnios	4	(7.8)	1	(6.3)	3	(8.6)	0.775
Preeclampsia	1	(2.0)	0	(0.0)	1	(2.9)	0.495
Abnormal location of placenta (accreta, increta, percreta, or previa)	9	(17.6)	4	(25.0)	5	(14.3)	0.352
Breech position of the fetus	1	(2.0)	1	(6.3)	0	(0.0)	0.135
Multiple births (twin, triplet, etc.)	5	(9.8)	0	(0.0)	5	(14.3)	0.111
Fetal distress or compromise	2	(3.9)	0	(0.0)	2	(5.7)	0.329
Cephalopelvic disproportion	5	(9.8)	2	(12.5)	3	(8.6)	0.662
Small fetus for gestational age	3	(5.9)	0	(0.0)	3	(8.6)	0.227
Preterm premature rupture of membranes	1	(2.0)	0	(0.0)	1	(2.9)	0.495
Preterm contraction	3	(5.9)	0	(0.0)	3	(8.6)	0.227
Wanted by mother	2	(3.9)	1	(6.3)	1	(2.9)	0.562
Amount of propofol used (mg)					624.0	±277.9	(−)
Amount of remimazolam used (mg)			107.2	±34.3			(−)
Operation time (min)	93.8	±18.6	99.8	±25.5	91.1	±14.1	0.276
Anesthesia time (min)	120.2	±21.9	125.9	±25.4	117.6	±19.9	0.253
Known risk factors of PPH							
Old age of mother	17	(33.3)	5	(31.3)	12	(34.3)	0.831
Obesity before pregnancy	2	(3.9)	1	(6.3)	1	(2.9)	0.562
Known coagulation defect	0	(0.0)	0	(0.0)	0	(0.0)	(−)
High parity	18	(35.3)	8	(50.0)	10	(28.6)	0.137
Nulliparity	23	(45.1)	7	(43.8)	16	(45.7)	0.896
History of PPH	0	(0.0)	0	(0.0)	0	(0.0)	(−)
Abnormal location of placenta	8	(15.7)	3	(18.8)	5	(14.3)	0.684
Intrapartum bleeding	6	(11.8)	4	(25.0)	2	(5.7)	0.047
Intrapartum use of magnesium sulfate	0	(0.0)	0	(0.0)	0	(0.0)	(−)
Delayed delivery	0	(0.0)	0	(0.0)	0	(0.0)	(−)
Polyhydramnios	0	(0.0)	0	(0.0)	0	(0.0)	(−)
Twins or multiple gestations	4	(7.8)	0	(0.0)	4	(11.4)	0.159
Macrosomia	1	(2.0)	0	(0.0)	1	(2.9)	0.495
Outcomes							
Insufficient contraction	24	(47.1)	5	(31.3)	19	(54.3)	0.126
Number of intraoperative uterotonics used	2.4	±0.7	2.1	±0.7	2.5	±0.7	0.108
Oxytocin	51	(100.0)	16	(100.0)	35	(100.0)	(−)
Carbetocin	42	(82.4)	12	(75.0)	30	(85.7)	0.352
Sulprostone	27	(52.9)	6	(37.5)	21	(60.0)	0.135
Methylergometrine	0	(0.0)	0	(0.0)	0	(0.0)	(−)
EBL >300 mL, assessed by obstetricians	3	(5.9)	0	(0.0)	3	(8.6)	0.227
EBL assessed by anesthesiologists (mL)	729.4	±432.7	787.5	±309.6	702.9	±480.3	0.218
PPH	2	(3.9)	1	(6.3)	1	(2.9)	0.562
Uterine atony	0	(0.0)	0	(0.0)	0	(0.0)	(−)
Postoperative LOS (days)	4.8	±0.9	4.5	±1.2	5.0	±0.7	0.008

Continuous variables are presented as means ± SDs, while categorical variables are presented as numbers (percentages). If the *P*-value is < 0.05, it indicates a significant difference in the mean or frequency between the remimazolam and propofol groups. The chi-squared test was used for binary variables and Student's t-test for normally distributed data (age and BMI). For data that did not follow normal distribution, the Mann–Whitney *U* test was used as a nonparametric statistical method. SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; PPH, postpartum hemorrhage; EBL, estimated blood loss; LOS, length of hospital stay.

decided whether additional uterotonics (carbetocin 100 μg, methylergometrine 0.2 mg, or sulprostone 1000 μg) were necessary. All mothers were already injected with oxytocin immediately after delivery, but upon the first assessment of the obstetrician immediately after delivery (within 2–3 min of delivery), if sufficient uterine contractions were not guaranteed, carbetocin was additionally administered. If oxytocin/carbetocin failed to sufficient uterine tone, made the decision to administer the second-line uterotonics at the second assessment (5 min after delivery). In the case of ergometrine, the obstetrician checked the patient's blood pressure and considered administering it if there was no hypertension. If an inadequate uterine tone persisted even after ergometrine administration, the obstetrician considered the administration of sulprostone. Once satisfactory uterine contractions were confirmed by the obstetrician, the incised uterus and abdomen were sutured to complete the surgery. After the complete reversal of neuromuscular blockade, the patient was extubated and monitored closely for 1 h in the recovery room. A gauze pad was placed under the patient to detect any abnormal hemorrhage, and the pad weight was measured hourly to determine the volume of bleeding. If excessive bleeding occurred, additional treatment and procedures were performed by the obstetrician [9].

The demographic characteristics and preoperative comorbidities of the patients were extracted using data from preoperative evaluation records stored as electronic medical records. The risk factors for PPH including old age of the mother (>35 years), obesity before pregnancy (body mass index [BMI] >30 kg/m^2), known coagulation defects, high parity (≥3), nulliparity, history of PPH, abnormal location of placenta (accreta, increta, percreta, or previa), intrapartum bleeding, intrapartum use of magnesium sulfate, delayed delivery, polyhydramnios, twins or multiple gestations, and macrosomia, were collected [10,11]. Anesthesia records were reviewed to determine the number of uterotonic agents administered to each patient during surgery. The EBL estimated by the obstetrician was determined from the patients' surgical records. In addition, the EBL measured by an anesthesiologist was collected from the anesthesia records. Postoperative LOS and the occurrence of PPH or uterine atony were also recorded. Data collection was performed by the Medical Information Team at Korea University Anam Hospital. All data will be made available upon reasonable request.

Statistical analyses were performed using SPSS software (Version 20.0; IBM, Chicago, IL, USA). The data were expressed as means ± standard deviations, medians (25th and 75th percentiles), or the number of patients (%). Two-tailed *P*-values were presented, and a *P*-value <0.05 was considered statistically significant. The patients were classified into two groups based on the maintenance agents used: propofol or remimazolam group. Differences in characteristics between the two groups were compared using the chi-square test, Student's t-test, or Mann–Whitney *U* test. A binary logistic regression analysis was performed to assess the differences in the effects of the anesthetic agent, while excluding the effects of confounding variables, which are risk factors for uterine atony. Statistical analyses were performed in collaboration with the Department of Biostatistics at the Korea University College of Medicine.

3. Results

Data were collected from a total of 51 patients over a period of 17 months, with 35 and 16 patients in the propofol and remimazolam groups, respectively. Given its recent introduction, remimazolam is a less well-known anesthetic agent relative to propofol, which is used more frequently. Table 1 summarizes the characteristics and demographics of the patients included in this study. The risk factor for PPH demonstrating a significant difference between the remimazolam and propofol groups was the incidence of intrapartum bleeding ($P = 0.047$). In the propofol group, 66.7% of patients belonged to the MU category, while only 14.3% of the remimazolam group fell into the MU category. In the remimazolam group, a higher number of patients experienced uterine bleeding during pregnancy (n = 4, 25.0%) as compared to the propofol group (n = 2, 5.7%). Risk factors for PPH, such as known coagulation defects, history of PPH, intrapartum use of magnesium sulfate, delayed delivery, and polyhydramnios, were not identified in all patients. The remaining risk factors did not show a significant difference between the two groups.

Only one patient in each group (a total of two patients) experienced PPH. Following PPH, one patient in the remimazolam group was administered oxytocin and 2 mg methylergometrine the day after delivery because of PPH followed by uterine artery embolization. The other patient in the propofol group was diagnosed with uterine atony, and a 5.3-mm Foley catheter with a 25-mL balloon was inserted into the vagina to control the hemorrhage.

Twenty-four patients were categorized as having MU, while 27 patients only used FU (Table 1). None of the patients received

Table 2
Correlation between the use of remimazolam and clinical outcomes confirmed by regression analysis (forced entry).

Outcomes	*P*-value	Odds ratio	95% confidence interval			R^2
Insufficient contraction	0.224	0.390	0.075	to	1.782	0.201
EBL >300 mL, assessed by obstetricians	0.998	0.000	ND			0.154
PPH	1.000	3.233	ND			0.282
Uterine atony	ND	ND	ND			ND
Outcomes	***P*-value**	**Coefficient**	**95% confidence interval**			**Adjusted R^2**
Number of intraoperative uterotonics used	0.202	−0.293	−0.748	to	0.163	0.069
EBL assessed by anesthesiologists (mL)	0.327	146.617	−151.620	to	444.853	−0.006
Postoperative LOS (days)	0.134	−0.453	−1.052	to	0.146	0.020

For continuous outcomes, linear logistic regression analyses were performed. The adjusted R squared was added to account for the proportion of variance in the dependent variable. For binary outcomes, binary logistic regression analysis was performed and Cox and Snell's R squared was displayed. EBL, estimated blood loss; PPH, postpartum hemorrhage; LOS, length of hospital stay.

methylergometrine during the cesarean section. Five of 16 patients (31.3%) in the remimazolam group received MU, whereas 19 of 35 patients (54.3%) received MU in the propofol group. The chi-square test revealed no significant differences in rate of MU between the two groups ($P = 0.126$). Additionally, the number of uterotonics used did not differ between the remimazolam and propofol groups (2.1 ± 0.7 vs 2.5 ± 0.7, $P = 0.108$).

The precise numeric values for secondary outcomes are provided in Table 1. An EBL over 300 mL estimated by the obstetrician was recorded in none of the patients in the remimazolam group and in three patients in the propofol group ($P = 0.227$). The type of maintenance agent was not associated with the anesthesiologist-estimated EBL (787.5 ± 309.6 mL vs 702.9 ± 480.3 mL, $P = 0.218$). However, the remimazolam group had a hospitalization duration of 4.5 ± 1.2 days and the propofol group had a hospitalization duration of 5.0 ± 0.7 days, showing a significant difference in the LOS between the two groups ($P = 0.008$).

A regression analysis was conducted to confirm the independent association between clinical outcomes and the type of maintenance agents used while accounting for the influence of risk factors for PPH. The results of the regression analysis, considering all variables, are presented in Table 2. None of the 51 patients were diagnosed with uterine atony; therefore, we could not analyze the difference in the incidence of atony between the two groups. As a result, we could not conclude if the use of remimazolam significantly changed the risk of clinical outcomes. Overall, the goodness-of-fit of the regression model was low.

After removing insignificant variables using the backward Wald test, abnormal placental location ($P = 0.079$, odds ratio = 5.004) and the use of remimazolam ($P = 0.100$, odds ratio = 0.327) remained the most relevant factors for MU (Table 3A). Additionally, a linear regression analysis was performed using the number of uterotonics as the dependent variable. Similarly, abnormal placental location ($P = 0.056$) and the use of remimazolam ($P = 0.081$) were identified as the most related independent variables (Table 3B). The use of remimazolam may have reduced the number of uterotonics used by −0.354. However, these two most highly correlated variables were not statistically significant.

The linear regression analysis with backward selection showed that the use of remimazolam was not significantly associated with EBL. Additionally, remimazolam use was not associated with the incidence of PPH in this analysis. Only the use of remimazolam emerged as a factor most related to the postoperative LOS (Table 3C). The use of remimazolam, although not statistically significant, demonstrates clinical relevance as it may potentially shorten the postoperative LOS by approximately half a day ($P = 0.059$, unstandardized coefficient −0.500).

4. Discussion

This study investigated the use of uterotonic agents during cesarean sections under general anesthesia to compare uterine contractility between mothers who received remimazolam and those who received propofol. In terms of clinical indicators, such as the number of uterotonics used, volume of bleeding, and length of hospitalization, the use of remimazolam did not demonstrate a significant increase in these outcomes when compared to the use of propofol. In particular, the administration of remimazolam instead of propofol suggested the possibility for reducing the LOS after cesarean section.

In this study, there was no significant difference in the proportion of patients who used more uterotonic agents between the remimazolam and propofol groups. There was also no difference in the number of uterotonics used, intraoperative blood loss, or the rate of PPH between the two groups. The postoperative LOS was significantly shorter in the remimazolam group than in the propofol group. Even when assessing risk through regression analysis rather than simple comparisons, clinical indicators such as uterotonics usage and EBL did not significantly increase with the use of remimazolam. However, the possibility of shortening the postoperative LOS after cesarean section was suggested by administering remimazolam instead of propofol.

Based on a pilot study involving 16 participants, it was inferred that with a sample size of 37 participants in main study, significant results could be obtained through the chi-square test regarding the hypothesis. However, the chi-square test revealed no significant difference in the rates of MU between the two groups (remimazolam group 31.3% vs. propofol group 54.3%, P = 0.126). Several hypotheses can be considered here. Firstly, the condition of the single obstetrician during the data collection period might have been

Table 3
Selected variables by stepwise regression analysis (Wald test, backward elimination) that influence (A) the risk of insufficient uterine contraction, (B) the number of uterotonics used, and (C) the postoperative length of stay.

(A)

Final-selected variables	*P*-value	Odds ratio	95% confidence interval
Abnormal location of placenta	0.079	5.004	0.830 to 30.160
Use of remimazolam	0.100	0.327	0.086 to 1.238

(B)

Final-selected variables	*P*-value	Coefficient	95% confidence interval
Abnormal location of placenta	0.056	0.497	−0.013 to 1.007
Use of remimazolam	0.081	−0.354	−0.754 to 0.046

(C)

Final-selected variables	*P*-value	Coefficient	95% confidence interval
Use of remimazolam	0.059	−0.500	−1.020 to 0.020

unique. Since the obstetrician in this study ceased all surgeries as of August 31, 2022, he might have adopted a more cautious approach toward uterotonics usage in the latter part of this study. Additionally, the 18-month period of data collection saw an increase in the rate of remimazolam use over time, which might have contributed to a higher rate of MU in the remimazolam group. Secondly, as a retrospective study, there is a possibility that the severity of patients in the remimazolam group and the propofol group were slightly different. It is possible that patients with a higher severity used remimazolam. Remimazolam was more frequently used in patients with intrapartum bleeding or in those with a higher BMI. In cases where the BMI is higher, there is a greater likelihood of opting for remimazolam to facilitate better preservation of spontaneous breathing. Additionally, the use of remimazolam in patients with reported intrapartum bleeding may have contributed to the elevated rates of MU. Whatever the hypothesis, a prospective study with the same hypothesis will be needed to overcome these drawbacks.

None of the drugs used to maintain general anesthesia have demonstrated significant superiority thus far. The current guidelines for clinical practice suggest the use of a combination of midazolam, fentanyl, remifentanil, inhalation agents, and nitrous oxide. In this study, we observed the potential of remimazolam as a maintenance agent for general anesthesia after delivery. Remimazolam, a short-acting benzodiazepine, can be used for both sedation and general anesthesia [12]. General anesthesia can be induced within 2 min [12], with consciousness typically restored within 15 min [3]. Unlike propofol, it has the advantage of being reversible. Flumazenil can be used as a reversal agent in instances of overdose [13].

The typical duration of a cesarean section is usually less than 1 h [14,15]. The administration of benzodiazepines, opioids, or nitrous oxide after delivery can sufficiently maintain unconsciousness within this timeframe [1]. However, the average operation time of the attending obstetrician participating in this study was 93.8 $\pm$ 18.6 min, which was longer than that reported in previous studies. This extended surgical time can be attributed in part to the characteristics and proficiency level of the obstetrician, or in the case of high-risk pregnancies that require general anesthesia, the surgery time tends to be longer. Considering these factors, propofol, which has an excellent recovery profile [16] and the ability to reduce postoperative nausea and vomiting [17], had been used routinely to maintain general anesthesia instead of short-acting benzodiazepines or low-concentration volatile anesthetics. Propofol is widely recognized as a standard agent for inducing anesthesia in cesarean sections [18,19]. However, its application in studies concerning uterine contractions remains a subject of debate. In animal studies [20] and investigations on isolated human uterine smooth muscle [21], propofol demonstrated a notable suppression of uterine contractions. While propofol induces less relaxation in uterine muscles compared to volatile anesthetics [22], it remains crucial to acknowledge the potential decrease in uterine contractility associated with continuous propofol infusion.

In our study, following the induction of general anesthesia, sevoflurane was used to maintain anesthesia prior to delivery. The use of thiopental and sevoflurane may by itself interfere with the uterine contractions. Even if intravenous agents were started after confirming the end of inhalational anesthesia, residual effects cannot be excluded. These clinical situations contribute to the complexity of interpreting the primary outcome. However, this protocol was developed using caution in view of the limited understanding of the effects of remimazolam on fetuses. Given that general anesthesia in pregnant patients requires rapid induction and neuromuscular blockade, thiopental and succinylcholine are commonly used [23]. Midazolam, a benzodiazepine, is less frequently utilized as an induction agent compared to thiopental because of its slower onset and the possibility of depression in infants [18,24]. A more optimal study design would entail avoiding the exposure of patients in the remimazolam group to thiopental and sevoflurane. To this end, the potential of remimazolam as an anesthesia-inducing drug for cesarean sections should be explored in future studies.

Remimazolam has pharmacological properties that affect the gamma aminobutyric acid A (GABAA) receptor, similar to midazolam [25]. Among the subunits of the GABAA receptor, the gamma 2 subunit is known to bind to benzodiazepines [26]. Importantly, GABAA receptors are abundantly distributed in the uterine myometrium [27], and the inhibitory action of progesterone on uterine contraction operates through the GABAA system [28]. In contrast to GABAB receptors, stimulation of GABAA receptors inhibited uterine muscle contraction in rabbits [27]. Since remimazolam is also known to bind to GABAA, it may be involved in an unknown uterine contraction inhibitory response. From the results of this study, it was inferred that there might be no noticeable suppression of the uterine contraction pattern because the amount of uterotonics used is less than that of propofol, but this is not certain. Further laboratory studies focusing on remimazolam and myometrium are needed to address this issue, given the methodological constraints of this study.

A notable limitation of this study is its retrospective nature. Since this is a retrospective study rather than an RCT, the reliability of the data is not sufficient and it is accompanied by many biases. The findings may reflect differences between innovative anesthesiologists who prefer remimazolam and more conservative ones who prefer propofol. While this study indicates remimazolam could be as effective as other anesthetics for cesarean sections, additional prospective studies are needed to validate the results. Second, based on the previous pilot sample of 16 patients, we acknowledge that the power analysis may not have been as robust as desired. This study received consultation from the Department of Medical Statistics at Korea University Anam Hospital, and it was confirmed that data from a total of 33 patients would be needed. Unfortunately, our ambitious plan to achieve statistically significant results for the primary outcome in 33 patients failed. Nonetheless, our study holds significance as the first report on the application of remimazolam in cesarean sections pointing to, though not proving, a possible reduction in the postoperative LOS. On these grounds, we are planning a prospective study based on these preliminary insights. Third, we could not identify cases of uterine atony. Because of the very low incidence of atony, we tried to estimate the risk of insufficient uterine contraction through the number of uterotonics used as the primary outcome. However, the degree of uterine contraction cannot be accurately determined by counting the drugs used during caesarean section. The number and type of uterotonics our institution uses was not representative of many countries' practices. If a larger number of participants were included, a difference in the incidence of uterine atony may be identified.

In conclusion, despite the remaining uncertainties regarding its risks, remimazolam could be considered as a potential new agent for general anesthesia in cesarean sections. Since this study suggests the possibility of reducing the LOS for mothers after cesarean sections, experimental research on maternal subjects is required to determine the molecular and biological mechanisms. Due to the

inherent limitations of the present study design, the present results cannot rule out all adverse reactions to remimazolam during obstetric anesthesia. Future prospective randomized controlled studies should reaffirm the advantages and disadvantages of remimazolam by comparing it with other general anesthetic agents to provide high-quality evidence.

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Data availability statement

Sharing research data helps other researchers evaluate your findings, build on your work and to increase trust in your article. We encourage all our authors to make as much of their data publicly available as reasonably possible. Please note that your response to the following questions regarding the public data availability and the reasons for potentially not making data available will be available alongside your article upon publication. Has data associated with your study been deposited into a publicly available repository?

⇨ No.

Sharing research data helps other researchers evaluate your findings, build on your work and to increase trust in your article. We encourage all our authors to make as much of their data publicly available as reasonably possible. Please note that your response to the following questions regarding the public data availability and the reasons for potentially not making data available will be available alongside your article upon publication. Has data associated with your study been deposited into a publicly available repository?

⇨ Data will be made available on request.

This study has not been published previously.

CRediT authorship contribution statement

Eunji Ko: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Sung Uk Choi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Jaehee Lee:** Writing – review & editing, Validation, Software, Formal analysis, Data curation, Conceptualization. **Eun-Saem Choi:** Writing – review & editing, Validation, Investigation, Funding acquisition, Conceptualization. **Yoon Sun Park:** Writing – review & editing, Visualization, Software, Resources, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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