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ORIGINAL ARTICLE

The comparison of caesarean section bleeding between volatile and total intravenous anaesthesia in a Japanese nationwide database

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BACKGROUND Volatile anaesthesia may increase blood loss because of the uterine-relaxing effect of the volatile anaesthetics during caesarean section under general anaesthesia.

OBJECTIVE This study compared the bleeding risk during caesarean section between volatile anaesthesia and total intravenous anaesthesia (TIVA) using a nationwide inpatient database in Japan.

DESIGN Observational study.

SETTING Nationwide inpatient database in Japan from April 2012 to March 2020.

PATIENTS Women who underwent caesarean section under general anaesthesia.

MAIN OUTCOME MEASURES Volume of blood loss.

RESULTS We identified 26 585 women, including 19 320 in the volatile anaesthesia group (mean age = 32.9 ± 5.5 years) and 7265 in the TIVA group (mean age = 32.8 ± 5.5 years). The mean blood loss was 1113 ± 909 and 1136 ± 944 ml and the proportion of blood transfusion was 14.7 and 16.0% in the volatile and TIVA groups, respectively. With conventional regression analyses, volatile anaesthesia was associated with a slightly lower risk of bleeding: the adjusted mean difference for blood loss (95% CI) was −56.1 (−81.4 to −30.7). However, in the instrumental variable analysis, volatile anaesthesia was associated with a higher risk of bleeding: adjusted mean difference for blood loss (95% CI) was 154.3 (112.4 to 196.3) ml.

CONCLUSION This large observational study with instrumental variable analyses suggested an increased bleeding risk associated with volatile anaesthesia, and the results were not identical to those in the conventional regression analyses.

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KEY POINTS

- Is volatile anaesthesia associated with an increase in caesarean section bleeding because of its uterine-relaxing effect?
- In the conventional regression analyses, the volume of blood loss and proportion of blood transfusion were slightly lower in the volatile anaesthesia group than in the total intravenous anaesthesia group; however, the instrumental variable analyses showed that volatile anaesthesia was associated with an increased risk of bleeding.
- Using a nationwide observational database in Japan, our instrumental variable analyses suggested an association between volatile anaesthesia and increased risk of caesarean section bleeding, which is in line with its physiological mechanism of uterine relaxation.

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Introduction

Maternal death during the perinatal period is still a worldwide problem,[1,2] and the risk of caesarean section performed under general anaesthesia is higher than that of regional anaesthesia.[3] General anaesthesia for caesarean section is usually used in emergency situations, failures of regional anaesthesia, or situations in which regional anaesthesia is contraindicated.[4] There are two types of general anaesthesia: volatile anaesthesia and total intravenous anaesthesia (TIVA). The choice of the type of general anaesthesia is at the discretion of the anaesthesiologist.[4]

There are some reports of uterine relaxation by volatile anaesthetics in animal studies and studies using tissue fragments of the human pregnant uterus.[5–7] Meanwhile, propofol, which is often used in TIVA, was reported not to decrease the uterine tone at clinically relevant concentrations.[8] Therefore, some anaesthesiologists believe that, compared with TIVA, volatile anaesthesia may increase blood loss during caesarean section.[9–11] Bleeding and the associated maternal death are the main risks in caesarean sections,[12] therefore, information on the association between volatile anaesthesia and bleeding risk could help anaesthesiologists in the selection of the type of general anaesthesia to use in clinical practice.

However, to date, there has been a lack of human studies on this topic. To our knowledge, only a small, randomised control trial ($n = 40$) conducted approximately 30 years ago showed no difference in blood loss at delivery between volatile anaesthesia and TIVA during caesarean section under general anaesthesia.[13] Therefore, a contemporary large-scale data analysis is warranted. This study aimed to compare the blood loss during caesarean section between volatile anaesthesia and TIVA, using a large database of hospitalised patients in Japan. We hypothesised that, compared with TIVA, volatile anaesthesia may increase blood loss because of its uterine-relaxing effect.

Materials and methods

Ethics

Ethical approval for this study (3501-(3)) was provided by the Institutional Review Board of the University of Tokyo, Bunkyo-ku, Tokyo (Chairperson Prof A. Akabayashi) on 25 December 2017. The requirement for informed consent was waived as the anonymity of the data was maintained.

Data Sources

This was a retrospective cohort study using the Diagnosis Procedure Combination database, a Japanese national administrative claims and discharge abstract database.[14,15] Many medical studies have been conducted using this database.[16–19] The data recorded in the database includes hospital identifiers, age, height, weight, diagnosis and comorbidities at the time of admission, and complications that occur after admission. The diseases are classified according to the *International Classification of Diseases, 10th Edition* (ICD-10) codes. Perinatal information includes gestational age at admission, birth weight and blood loss at delivery. The database also includes admission and discharge dates, discharge status, dates and doses of all drugs and blood products administered, surgery, anaesthesia and other procedures performed. All interventional and surgical procedures are registered with Japan-specific codes.

Study population

We identified women who underwent caesarean section (Japanese medical procedure codes K8981–K8983) from 1 April 2012 to 3 March 31 2020. A caesarean section under general anaesthesia was identified with insurance claims for general anaesthesia (Japanese medical procedure codes L0081–L0085) and muscle relaxants (succinylcholine, rocuronium, vecuronium or pancuronium) used on the day of delivery. We excluded women with an insurance claim for general anaesthesia but no insurance claim for muscle relaxants on the day of delivery because they may have received regional anaesthesia (spinal or epidural anaesthesia) under sedation. Additionally, data for the following women were excluded from the analysis: women who had no data on any of the following: blood loss at delivery, height, weight, gestational age at delivery and those who received blood transfusions before the day of delivery.

Definition of the groups

The women were assigned to the volatile anaesthesia group if there were insurance claims for volatile anaesthetics (sevoflurane, desflurane, isoflurane or halothane) on the day of delivery. The other women were assigned to the TIVA group.

Outcomes

The primary outcome of interest was blood loss at delivery. The secondary outcome was blood transfusions (red blood cells, fresh frozen plasma or platelet transfusions) on the day of delivery.

Statistical analysis

We conducted conventional analyses first (i.e., adjusted comparison using regression models and one-to-one propensity score-matched analysis) to compare the two groups. For descriptive purposes, continuous variables were presented as mean ± SD, and categorical variables were presented as number (%). The balance of variables between the two groups was quantified using the absolute standardised difference.[20]

We performed multivariable regression analyses for blood loss at delivery and multivariable logistic regression analyses for blood transfusions in women on the day of delivery. Based on our clinical knowledge and the

previous literature,[21–25] we extracted covariates, which could affect bleeding as potential confounding factors. These included patient characteristics (age, BMI and period of delivery), obstetric characteristics/comorbidities (gestational age at delivery, abnormal placentation, multiple gestations, previous caesarean section and/or history of uterine surgery, uterine leiomyoma, infection of amniotic sac and membranes, gestational hypertension and preeclampsia/eclampsia), other complications (anaemia, thrombocytopenia/coagulopathy, hypercoagulable state, pre-existing hypertension, diabetes mellitus, chronic ischaemic heart disease, chronic congestive heart failure, cardiomyopathy, congenital heart disease, valvular disease, pulmonary hypertension, asthma, chronic liver disease, chronic renal disease, malignancy, history of organ transplant and HIV infection) and hospital characteristics (annual number of caesarean sections and caesarean sections under general anaesthesia). Obstetric characteristics/comorbidities and the other comorbidities were defined based on ICD-10 codes (shown in Supplemental Digital Content 1, http://links.lww.com/EJAIC/A28).

We established the following three models: model 1 to adjust for age only (four groups, <25, 25–34, 35–39 and ≥40 years); model 2 to adjust for the age, BMI (four groups, <18.5, 18.5–24.9, 25.0–29.9 and ≥30.0 kg m^{-2}) and gestational age at delivery (six groups, <32, 32–36.9, 37–38.9, 39–40.9, 41–41.9 and ≥42 weeks); and model 3 to adjust for the age, BMI, period of delivery (four groups, 2014 March or earlier, 2014 April to 2016 March, 2016 April to 2018 March and 2018 April to 2020 March), and all the other potential confounding factors as mentioned above. We accounted for the clustering effect of hospitals (i.e. patients admitted to the same hospital may be more likely to have similar characteristics and outcomes than those admitted to different hospitals) in these models to estimate robust standard errors with generalised estimation equations.[26]

We performed a one-to-one propensity score-matched analysis as a sensitivity analysis to compare the two groups, considering their baseline differences. Propensity scores were estimated for individual patients using a multivariable logistic regression model, setting general anaesthesia type as the dependent variable. The independent variables included all variables that were used in model 3 of our main analysis. The C-statistic was calculated to evaluate the discriminatory power of the predictive model.[27] Nearest-neighbour matching in a 1 : 1 ratio was then performed based on the estimated propensity scores. A match occurred when a woman in the volatile anaesthesia group had an estimated propensity score within a calliper width of 0.2 of the SD of the propensity score of a woman in the TIVA group. Absolute standardised differences were computed to examine the balance in the covariates between the two groups. An absolute standardised difference of less than 0.1 was considered balanced.[20] In the matched pairs of women, we compared outcomes between the two groups using the unpaired *t* test for blood loss at delivery and the chi-squared test for blood transfusions on the day of delivery.

Second, we performed instrumental variable analyses.[28] Instrumental variable analyses can, theoretically, cope with unmeasured confounding and estimate the strength of the causal relationship in observational datasets if an appropriate instrumental variable is used.[29] Instrumental variables must meet the following three conditions: (i) it has a causal effect on the exposure, (ii) it affects the outcome only through the exposure and (iii) there is no relationship between the patient characteristics and the instrumental variable.[30] We used the proportion of cases where volatile anaesthesia was used for caesarean section under general anaesthesia at each hospital (i.e. the facility preference) as the instrumental variable. The assumption (i) was quantitatively assessed using the *F*-statistic[31]: the instrumental variable was considered strongly associated with treatment allocation when *F*-statistic is greater than 10. The assumption (ii) cannot be quantitatively assessed, but the facility preference does not seem to affect the outcome directly, and it is indeed a common instrumental variable in epidemiological studies.[32] The assumption (iii) was assessed by examining the associations between the instrumental variable and the measured confounders. If associations between the instrumental variable and some confounding factors exist, it is recommended that the instrumental variable analysis additionally controls for these factors.[33]

We used the two-stage least squares method for blood loss at delivery and the two-stage residual inclusion method for blood transfusions on the day of delivery without any adjustment for covariates (i.e. crude model). In addition, we compared the patient characteristics by dichotomising the study participants according to the median of the instrumental variable (the proportion of volatile anaesthesia use at each hospital) and identified the unbalanced covariates, with an absolute standardised difference of greater than 0.1. If there were such variables, we additionally adjusted for these covariates in the models (i.e. adjusted model).[33]

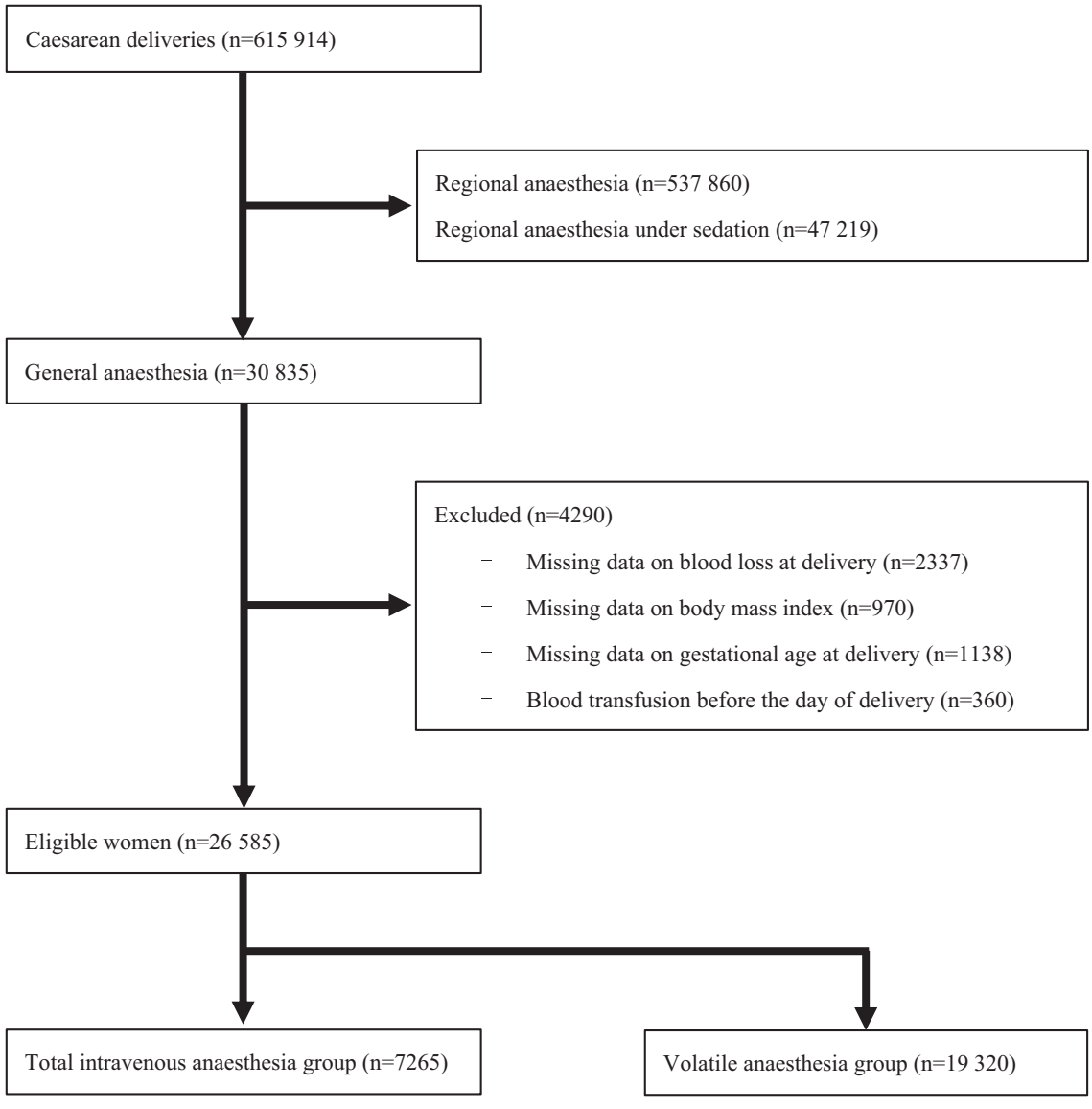
We used Stata version 17 (StataCorp, College Station, Texas, USA) for all statistical analyses in this study. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement.[34,35] All reported *P* values were two-sided, and *P* less than 0.05 was considered statistically significant.

Results

Participant selection and baseline characteristics

In the database, we identified 615 914 women who underwent caesarean sections during the study period.

Fig. 1 Flow chart of the recruitment of women.



Among them, 30 835 women had caesarean section under general anaesthesia. After the exclusion criteria, 26 585 women were finally included: 19 320 received volatile anaesthesia and 7265 received TIVA (Fig. 1). The characteristics of the women are shown in Table 1. There were some notable differences during the period of delivery (2014 March or earlier) and the annual number of caesarean sections under general anaesthesia (15–23.9 and ≥24) between the groups. Supplemental Digital Content 2, http://links.lww.com/EJAIC/A29 shows the relationship between the proportion of volatile anaesthesia use during caesarean section under general anaesthesia at each hospital and the annual number of caesarean sections under general anaesthesia.

Outcomes

The histograms of blood loss at delivery for each group are shown in Fig. 2. The mean blood loss in the volatile anaesthesia group was 1113.0 ± 909.3 ml, whereas that in the TIVA group was 1136.1 ± 944.0 ml. The frequency of blood transfusion was 14.7 and 16% in the volatile anaesthesia and TIVA groups, respectively.

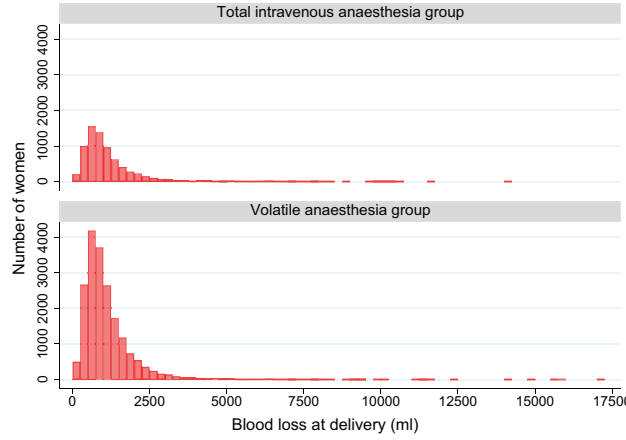
Table 2 shows the adjusted differences of blood loss and the adjusted odds ratios of blood transfusions on the day of delivery in the multivariable regression and multivariable logistic regression analyses, respectively. In all models, the volume of blood loss at delivery in the volatile anaesthesia group was significantly lower than that in the

Table 1 Characteristics of women receiving caesarean section under general anaesthesia

Covariates	Total intravenous anaesthesia group ($n = 7265$)	Volatile anaesthesia group ($n = 19\,320$)	Absolute standardised difference[a]
General characteristics			
Age (years)	32.8 ± 5.5	32.9 ± 5.5	
<25	527 (7.3)	1363 (7.1)	<0.01
25–34	3870 (53.3)	9993 (51.7)	0.03
35–39	2090 (28.8)	5763 (29.8)	0.02
≥40	778 (10.7)	2201 (11.4)	0.02
Body mass index (kg m^{-2})	25.1 ± 5.8	25.1 ± 4.9	
<18.5	195 (2.7)	545 (2.8)	<0.01
18.5–24.9	4026 (55.4)	10 657 (55.2)	<0.01
25.0–29.9	2178 (30.0)	5679 (29.4)	0.01
≥30.0	866 (11.9)	2439 (12.6)	0.02
Period of delivery			
2014 (March) or earlier	2141 (29.5)	4634 (24.0)	0.12
2014 (April) – 2016 (March)	1871 (25.8)	5223 (27.0)	0.03
2016 (April) – 2018 (March)	1662 (22.9)	4973 (25.7)	0.07
2018 (April) – 2020 (March)	1591 (21.9)	4490 (23.2)	0.03
Obstetric characteristics/complications			
Gestational age at delivery (weeks)	35.6 ± 4.5	35.3 ± 4.5	
<32	1181 (16.3)	3512 (18.2)	0.05
32–36.9	2111 (29.1)	5610 (29.0)	<0.01
37–38.9	2125 (29.3)	5442 (28.2)	0.02
39–40.9	1443 (19.9)	3744 (19.4)	0.01
41–41.9	352 (4.9)	932 (4.8)	<0.01
≥42	53 (0.7)	80 (0.4)	0.04
Abnormal placentation	725 (10.0)	2047 (10.6)	0.02
Multiple gestation	290 (4.0)	872 (4.5)	0.03
Previous caesarean section and/or history of uterine surgery	809 (11.1)	2056 (10.6)	0.02
Uterine leiomyoma	320 (4.4)	741 (3.8)	0.03
Infection of the amniotic sac and membranes	336 (4.6)	1083 (5.6)	0.05
Gestational hypertension	155 (2.1)	475 (2.5)	0.02
Preeclampsia/eclampsia	890 (12.3)	2752 (14.2)	0.06
Other complications			
Anaemia	1261 (17.4)	3762 (19.5)	0.06
Thrombocytopaenia/coagulopathy	207 (2.9)	571 (3.0)	<0.01
Hypercoagulable state	68 (0.9)	186 (1.0)	<0.01
Preexisting hypertension	142 (2.0)	388 (2.0)	<0.01
Diabetes mellitus	550 (7.6)	1253 (6.5)	0.04
Chronic ischaemic heart disease	12 (0.2)	39 (0.2)	<0.01
Chronic congestive heart failure	30 (0.4)	95 (0.5)	0.01
Cardiomyopathy	1 (0.0)	6 (0.0)	0.01
Congenital heart disease	24 (0.3)	85 (0.4)	0.02
Valvular disease	20 (0.3)	41 (0.2)	0.01
Pulmonary hypertension	5 (0.1)	11 (0.1)	<0.01
Asthma	47 (0.7)	155 (0.8)	0.02
Chronic liver disease	48 (0.7)	121 (0.6)	<0.01
Chronic renal disease	16 (0.2)	73 (0.4)	0.03
Malignancy	63 (0.9)	101 (0.5)	0.04
History of organ transplant	5 (0.1)	24 (0.1)	0.02
HIV infection	2 (0.0)	13 (0.1)	0.02
Hospital characteristics			
Annual number of caesarean sections			
<140	1852 (25.5)	4704 (24.4)	0.03
140–209	1950 (26.8)	5120 (26.5)	<0.01
210–279	1575 (21.7)	4666 (24.2)	0.06
≥280	1888 (26.0)	4830 (25.0)	0.02
Annual number of caesarean sections under general anaesthesia			
<8	1873 (25.8)	5107 (26.4)	0.02
8–14	1797 (24.7)	4367 (22.6)	0.05
15–23	2180 (30.0)	4655 (24.1)	0.13
≥24	1415 (19.5)	5191 (26.9)	0.18

Data are presented as mean ± SD or number (%). [a] An absolute standardised difference of greater than 0.1 was considered to be imbalanced.

Fig. 2 Histograms of blood loss at delivery for the total intravenous and volatile anaesthesia groups.



TIVA group (model 1, adjusted difference −64.5 (95% CI, −91.4 to −37.7) ml; model 2, adjusted difference −61.8 (−88.4 to −35.2) ml; model 3, adjusted difference −56.1 (−81.4 to −30.7) ml. Similarly, the frequency of blood transfusions on the day of delivery was statistically significantly lower in the volatile anaesthesia group than in the TIVA group [model 1, adjusted OR 0.87 (95% CI, 0.81 to 0.95), $P = .001$; model 2, adjusted OR 0.87 (95% CI, 0.80 to 0.94), $P = .001$; model 3, adjusted OR 0.85 (95% CI, 0.79 to 0.93), $P < .001$]. Propensity score-matched analyses showed similar results (Supplemental Digital Content 3, http://links.lww.com/EJAIC/A30 and Supplemental Digital Content 4, http://links.lww.com/EJAIC/A31). The C-statistic for goodness was 0.58 (95% CI, 0.57 to 0.59).

Table 3 shows the difference in blood loss and the odds ratios of blood transfusions on the day of delivery in the crude and adjusted models of instrumental variable analyses. The *F*-statistic was 12 092.9. There were almost no associations between the instrumental variable and the measured confounders, except for the annual number of caesarean sections and the annual number of caesarean sections under general anaesthesia (Supplemental Digital Content 5, http://links.lww.com/EJAIC/A32). Therefore, additional adjustments were done for these two variables. Contrary to the results of the conventional regression and propensity score analyses, the instrumental variable analyses showed that volatile anaesthesia was associated with an increased risk of blood loss [crude model, difference 150.7 (95% CI, 109.6 to 191.9) ml; adjusted model, difference 154.3 (112.4 to 196.3) ml]. Similarly, blood transfusions on the day of delivery in the volatile anaesthesia group were significantly higher than that in the TIVA group [crude model OR 1.23 (95% CI, 1.07 to 1.41), adjusted model OR 1.38 (1.20 to 1.59)].

Discussion

In this Japanese national database study, the blood loss at delivery and the frequency of blood transfusion were slightly lower in the volatile anaesthesia group than that

Table 2 **Adjusted differences in blood loss at delivery and adjusted odds ratios of blood transfusions on the day of delivery in different models using generalised estimation equations to adjust for within-hospital clustering**

	Blood loss at delivery		Blood transfusions on the day of delivery	
	Adjusted mean difference (ml, 95% CI)[a]	*P* value	Adjusted OR (95% CI)[b]	*P* value
Model 1[c]	−64.5 (−91.4 to −37.7)	<0.001	0.87 (0.81 to 0.95)	0.001
Model 2[d]	−61.8 (−88.4 to −35.2)	<0.001	0.87 (0.80 to 0.94)	0.001
Model 3[e]	−56.1 (−81.4 to −30.7)	<0.001	0.85 (0.79 to 0.93)	<0.001

CI, confidence interval; OR, odds ratio. [a] Blood loss at delivery in the volatile anaesthesia group minus blood loss at delivery in the total intravenous anaesthesia group. [b] The odds of blood transfusions on the day of delivery in the volatile anaesthesia group divided by the odds of blood transfusions on the day of delivery in the total intravenous anaesthesia group. [c] Model 1: age (four groups; <25, 25–34, 35–39, ≥40 years) adjusted. [d] Model 2: age (four groups; <25, 25–34, 35–39, ≥40 years), BMI (four groups; <18.5, 18.5–24.9, 25.0–29.9, ≥30.0 kg m^{-2}) and gestational age at delivery (six groups; <32, 32–36.9, 37–38.9, 39–40.9, 41–41.9, and ≥42 weeks) adjusted. [e] Model 3: Age (four groups; <25, 25–34, 35–39, ≥40 years), BMI (four groups; <18.5, 18.5–24.9, 25.0–29.9, ≥30.0 kg m^{-2}), period of delivery [four groups; 2014 (March) or earlier, 2014 (April)–2016 (March), 2016 (April)–2018 (March), 2018 (April)–2020 (March)], gestational age at delivery (six groups; <32, 32–36.9, 37–38.9, 39–40.9, 41–41.9, and ≥42 weeks), abnormal placentation, multiple gestation, previous caesarean section and/or history of uterine surgery, uterine leiomyoma, infection of amniotic sac and membranes, gestational hypertension, preeclampsia/eclampsia, anaemia, thrombocytopaenia/coagulopathy, hypercoagulable state, preexisting hypertension, diabetes mellitus, chronic ischaemic heart disease, chronic congestive heart failure, cardiomyopathy, congenital heart disease, valvular disease, pulmonary hypertension, asthma, chronic liver disease, chronic renal disease, malignancy, history of organ transplant, HIV infection, annual number of caesarean sections (four groups; <140, 140–209, 210–279, ≥280), and annual number of caesarean sections under general anaesthesia (four groups; <8, 8–14, 15–23, ≥24) adjusted.

Table 3 Instrumental variable analyses using the proportion of volatile anaesthesia use at each hospital as an instrumental variable

	Blood loss at delivery		Blood transfusions on the day of delivery	
	Mean difference (ml, 95% CI)[a]	*P* value	OR (95% CI)[b]	*P* value
Crude[c]	150.7 (109.6 to 191.9)	<0.001	1.23 (1.07 to 1.41)	0.004
Adjusted[d]	154.3 (112.4 to 196.3)	<0.001	1.38 (1.20 to 1.59)	<0.001

CI, confidence interval; OR, odds ratio. [a] Blood loss at delivery in the volatile anaesthesia group minus blood loss at delivery in the total intravenous anaesthesia group. [b] The odds of blood transfusions on the day of delivery in the volatile anaesthesia group divided by the odds of blood transfusions on the day of delivery in the total intravenous anaesthesia group. [c] Crude: no adjustment by covariates. [d] Adjusted: annual number of caesarean sections (four groups; <140, 140–209, 210–279, ≥280) and annual number of caesarean sections under general anaesthesia (four groups; <8, 8–14, 15–23, ≥24) adjusted. These are the variables for which absolute standardized difference were greater than 0.1 when women were separated by the median of the proportion of volatile anaesthesia use at each hospital and the characteristics of the women were compared.

in the TIVA group in the conventional regression and propensity score analyses. However, in the instrumental variable analyses, these differences were higher in the volatile anaesthesia group. The results from the instrumental variable analyses are consistent with our study hypothesis that volatile anaesthesia may increase blood loss because of the uterine-relaxing effect of the volatile anaesthetics.

To the best of our knowledge, there have been no clinical studies using large-scale data, which compare the choice of type of general anaesthesia and the blood loss during caesarean section. Observational studies are informative because it is generally difficult to conduct randomised controlled trials in the setting of an urgent caesarean section under general anaesthesia. In addition, as blood loss during caesarean section has a large SD and the frequencies of events related to blood loss are not high, it is reasonable to examine this using large-scale data.

The results from the conventional analyses and the instrumental variable analyses were in the opposite direction in the current study. According to a previous systematic review comparing propensity score and instrumental variable analyses, this phenomenon is often observed.[36] This review noted that 44% of the included studies reported conflicting results between the propensity score and instrumental variable analyses.[36] Moreover, the systematic review also suggests that the results of instrumental variable analyses were generally closer to the results of randomised clinical trials on the same topic. This was probably because of unmeasured confounding factors inherent in observational studies, which are difficult to remove by conventional regression analyses or propensity score analyses. In the current study, it is possible that some anaesthesiologists performed TIVA only for cases with a high risk of bleeding. However, data on the severity of placenta previa and the results of preoperative examinations are not available in the database. These unmeasured confounding factors cannot be removed by the conventional regression or propensity score analyses but may have been successfully removed by the instrumental variable analyses.

In the current study, the instrumental valuable (i.e. the hospital preference for volatile anaesthesia) was strongly associated with treatment allocation, with *F*-statistics being far more than 10. In addition, the hospital preference does not seem to affect the outcome directly. The characteristics of the women were almost the same when the patients were divided into two groups by the median value of the instrumental variable. The unbalanced variables (i.e. annual number of caesarean sections and the annual number of caesarean sections under general anaesthesia in the hospital) were additionally adjusted in the instrumental variable analyses. Finally, instrumental variable analyses generally require a 'monotonicity assumption', which means that all individuals in the study are assumed to be compliers.[37] In this study, the proportion of volatile anaesthesia use during caesarean section under general anaesthesia at each hospital may not violate the monotonicity assumption because the decision is most likely to be based on an anaesthesiologist's preference. Therefore, we consider that the instrumental variable is valid in the current study, providing results that are closer to the truth than the conventional regression and propensity score analyses, which suffer from the unmeasured confounding factors, such as the severity of placenta previa and the results of preoperative examinations.

The difference in blood loss we detected with instrumental variable analyses was approximately 150 ml higher in the volatile anaesthesia group than in the TIVA group in both the crude and adjusted models. This means that there was a difference of more than 10% in the mean blood loss. The frequency of blood transfusions was also higher in the volatile anaesthesia group than the TIVA group with an odds ratio of 1.23 in the crude model and 1.38 in the adjusted model. Therefore, the results were not only statistically significant but also clinically significant.

The results of our instrumental variable analyses are consistent with the results of preclinical studies that reported uterine muscle relaxation with volatile anaesthesia.[5,6,8] The results are also consistent with clinical studies that showed increased blood loss with the use of volatile anaesthetics during termination of pregnancy.[9–11] In contrast, a randomised controlled trial comparing blood loss at delivery as a secondary outcome reported no difference between volatile anaesthesia and TIVA.[13] However, this study had a small number of women ($n = 40$), and the difference between the two groups may not have been detected because of lack of power.

We acknowledge several limitations in this study. First, the primary outcome was defined as blood loss at delivery, but this measurement is generally difficult to perform, and visual assessment is very inaccurate and often includes amniotic fluid. However, such measurement error is most likely nondifferential; therefore, it would dilute the results to the null association between the exposure and outcome in the current study (meaning the true association would be even larger than the observed). To compensate for the uncertainty of the primary outcome, we also examined blood transfusions on the day of delivery as the secondary outcome, and this came to the same conclusion. Second, the concentrations of the volatile anaesthetics used during the caesarean section were unmeasured. As lower concentrations are generally recommended for use during caesarean section, it is possible that the effects of the volatile anaesthetics were underestimated by the use of lower concentrations. Conversely, a temporary high concentration of volatile anaesthetics may be used to obtain uterine relaxation, which may also have been related to the amount of blood loss.[38] However, there was a lack of data on the concentrations of volatile anaesthetics, preventing us from examining these hypotheses within the current study. Similarly, the blood concentrations of the intravenous anaesthetics were unmeasured. Third, this study did not include consideration of the use of opioids or other drugs during general anaesthesia. Finally, as there may be regional differences in practice and in the racial characteristics of the women affecting how they respond to anaesthetic drugs, the generalisability of our findings to other countries may be limited.[24,25]

Conclusion

Using a Japanese nationwide inpatient database, this large observational study with instrumental variable analyses suggested an increased bleeding risk associated with volatile anaesthesia, and this was not the same as found with conventional regression and propensity score analyses. Our findings suggest that anaesthesiologists should consider the bleeding risk associated with volatile anaesthesia when choosing the type of anaesthesia during caesarean section under general anaesthesia.

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