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ORIGINAL ARTICLE

EFFECT OF ANESTHETIC INDUCTION WITH PROPOFOL VERSUS THIOPENTAL ON OUTCOMES OF NEWBORNS AND WOMEN UNDERGOING CESAREAN SECTION: A PROPENSITY SCORE MATCHING ANALYSIS

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Abstract **Background:** We conducted a single-center retrospective study with propensity score matching to clarify which anesthetic agent, i.e., thiopental or propofol, provides better outcomes for newborns and women undergoing elective and/or urgent cesarean section with general anesthesia.

Methods: We collected maternal and fetal data (n=935) using obstetric and anesthetic charts of cesarean sections with general anesthesia between 1994 and 2013. After 1:1 propensity score matching with maternal age, body mass index, gestational period, fetal weight, type of surgery, pre-eclampsia, and fetal/maternal indication, we compared thiopental to propofol (n=392) regarding the following outcomes. The fetal primary outcome was their well-being evaluated by Apgar score (APS). The maternal primary outcome was the patient's hemodynamic changes due to tracheal intubation or delivery.

Results: The only APS at 1 min was significantly higher in the thiopental group. The other fetal outcomes such as APS at 5 minutes, the umbilical cord blood pH, and proportion of neonatal asphyxia after birth were similar between two groups. Regarding maternal outcomes, propofol significantly suppressed the increase in the patients' blood pressure from anesthetic induction to the delivery.

Conclusions: Our results indicate that propofol induction may be a first choice for cesarean section with general anesthesia.

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Key words: cesarean section; general anesthesia; propofol; thiopental; fetus.

Introduction

A safe anesthetic agent for cesarean sections should provide quick induction and stable maternal hemodynamics, and have a minimal effect on newborns. Based on these needs, thiopental has been a first-line anesthetic agent for cesarean sections since the 1930s[1]. In contrast, propofol, a very widely used anesthetic agent in other surgeries, is also thought to be suitable for cesarean sections[2] because of its rapid metabolism and excretion[3]. However, there is not much specific data showing which agent (thiopental or propofol) is safer for newborns and patients undergoing a cesarean section.

The results of randomized clinical trials (RCTs) investigating fetal and/or maternal outcomes in cesarean sections with general anesthesia by thiopental versus propofol[1, 3-10] indicate that propofol can result in less hypertension and/or tachycardia for mothers compared to thiopental. However, the results on fetal outcomes defined as Apgar scores (APS) and/or umbilical cord blood pH are controversial. Celleno et al.[4, 7] reported that neonates in the propofol group had lower APS values than those in the thiopental group, whereas a recent meta-analysis showed no significant difference in umbilical cord blood

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gas parameters or in APS between propofol and thiopental groups[11].

In addition to these claims, most of the studies investigating the outcomes of cesarean sections included only elective surgery[1, 3-9] with a small number of patients, although general anesthesia is required mostly in emergency cases. We thus felt that a clinical data analysis including a large number of patients with elective as well as urgent cases should be conducted. In the present study, to obtain such data, we performed a propensity score matching analysis using the clinical records of cesarean sections performed with general anesthesia over the past two decades at our hospital, and we then investigated which agent — thiopental or propofol — provides better outcomes for women who undergo cesarean sections and their newborns.

Patients and Methods

Data were obtained from obstetric and anesthetic charts of cases of cesarean sections with general anesthesia conducted at Hirosaki University Hospital between 1994 and 2013. After obtaining institutional ethical committee approval (approval no. 2014-079), we collected maternal and fetal demographic data including maternal age, height, weight, body mass index, gestational period, type of surgery (urgent or elective), indication of surgery (fetal or maternal indication), the number of patients with preeclampsia, the number of fetuses (single or twin or more), the dose of general anesthesia used, fetal weight, umbilical cord blood pH, APS at 1 and 5 minutes, induction-incision of skin (II) time, and induction-delivery (ID) time. The patients' intra-operative data including blood pressure (BP), heart rate (HR), the amount of fluids given and blood loss, and the incidences of failed intubation, hypotension, hypoxia, and transfusion were also collected. Hypotension was defined as systolic blood pressure ≤80 mmHg. Hypoxia was defined as saturation of percutaneous oxygen ≤90%. APS<7 was defined as neonatal asphyxia, and abnormal umbilical cord blood pH was defined as <7.2.

The anesthetic and surgical practice in the institution during the study period

In accordance with our institutional practice, almost all cesarean section was performed with general anesthesia until 2013. In the early study period (i.e.1994-2000), we mainly used thiopental for cesarean section because thiopental has been a first line agent since 1970s in our institution. But we began to use propofol after the year 2000 because propofol has been available in Japan since 1995. The surgical and obstetric practice such as indication of cesarean section wasn't changed during the study period.

The fetal outcomes

The primary fetal outcome was infant well-being evaluated by Apgar score. The umbilical cord blood pH and the II and ID times were used as secondary outcomes.

The maternal outcomes

The primary maternal outcome was the patient's hemodynamic changes due to tracheal intubation or delivery (i.e. delta BP or HR = peak value at tracheal intubation or at the delivery – baseline). The other intra-operative data associated with maternal safety such as the incidences of failed intubation, hypoxia, and hypotension were used as secondary outcomes.

Propensity score matching

We divided the patients into two groups according to the inductive anesthetics used: the propofol group and the thiopental group. First, an initial comparison of unmatched data was conducted. We then matched patients who received propofol or thiopental using the propensity score matching method. The propensity score

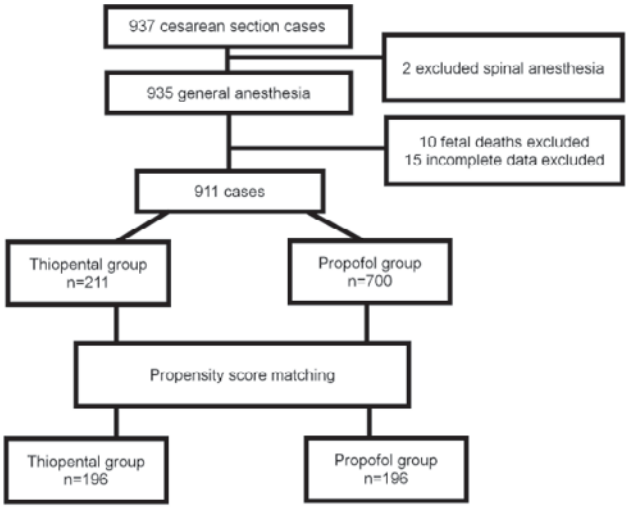

Fig 1. Flow diagram of this retrospective study with a propensity score matching analysis comparing thiopental with propofol

matching was conducted to consider selection biases as well as confounding factors between the two groups and to reduce them. We assessed the propensity score by performing a logistic regression including the following variables: maternal age, BMI, gestational period, fetal weight, type of surgery (elective or urgent), pre-eclampsia, and fetal/maternal indication. These possible variables were chosen for their potential association with the outcome of interest based on clinical knowledge. Goodness of fit for logistic model was assessed with the Hosmer-Lemeshow test. The patients were then matched 1:1 with the closest estimated propensity score. After the matching process, the two groups were compared regarding the outcomes of the patients and newborns described above.

Statistical analysis

For continuous variables with a normal distribution, the mean (± standard deviation [SD]) is reported. P-values <0.05 were considered significant. Student's *t*-test was used for continuous variables with normal distributions. The Mann-Whitney rank-sum test was used for continuous variables without a normal distribution. Categorical variables are presented as numbers and percentages. The comparison of qualitative variables was performed using Pearson's chi-square test or Fisher's exact test. All statistical analyses were conducted with IBM SPSS® statistics ver. 22.0 software (IBM, Tokyo).

Results

A total of 937 elective and urgent cesarean sections was performed between 1994 and 2013 at our hospital. Among them, 935 cases were performed with general anesthesia, and only two cases were performed with spinal anesthesia. The flow diagram of this retrospective analysis is given in Figure 1. Patients whose fetuses died before the patient's arrival in the operative suite (n=10) and incomplete data (n=14) were excluded. A total of 911 cases (thiopental induction, n=211; propofol induction, n=700) was analyzed. (Figure 1)

In the thiopental group, anesthesia was induced with thiopental at approx. 4.5 mg/kg, and the only thiopental was given until the delivery. Once the cord was clamped, patients were only given other anesthetic agents for maintenance. Most of the patients (88.6%) received neurolept anesthesia (NLA) for maintenance using nitrous

Table 1 The patients' characteristics

	Unmatched, n=911			Matched, n=392		
	Thiopental (n=211)	Propofol (n=700)	p-value	Thiopental (n=196)	Propofol (n=196)	p-value
Age, yrs	33.2±5.2	35.5±4.2	0.00	33.6±5.0	34.2±4.7	0.24
Gestation, weeks	33.8±5.0	33.5±5.3	0.50	33.8±5.0	33.3±5.5	0.47
Body weight, kg	60.9±9.0	63.5±11.0	0.00	61.0±9.0	61.3±8.6	0.77
Height, cm	157.8±5.3	158.1±5.4	0.50	157.8±5.2	158.0±5.6	0.75
BMI	24.4±3.4	25.4±4.0	0.00	24.5±3.4	24.5±3.2	0.85
Single/twin	182/29	634/66	0.07	169/27	176/20	0.28
(%)	(86.3/13.7)	(90.6/9.4)		(86.2/13.8)	(89.8/10.2)	
Surgical indication						
Elective/Urgent	39/171	336/364	0.00	39/156	30/166	0.22
N (%)	(18.6/81.4)	(48/52)		(20.0/80.0)	(15.3/84.7)	
Fetal indication N (%)	147 (69.7)	351 (50.2)	0.00	134 (68)	132 (67.7)	0.89
Maternal indication N (%)	95 (45)	461 (66)	0.00	92 (46.7)	99 (50.8)	0.45
Pre-eclampsia N (%)	14 (6.6)	55 (7.9)	0.55	14 (7.1)	20 (10.2)	0.28
Anesth agents						
Thiopental, mg	279.7±55.4	0	n.a.	282.0±55.9	0	n.a.
Propofol, mg	0	135.8±34.6	n.a.	0	134.3±37.5	n.a.
Sux, mg	51.5±9.6	54.5±12.0	0.00	51.5±9.6	53.0±11.7	0.17

N: number, BMI: body mass index, n.a.: not available, Sux: suxamethonium. Anesth: anesthetic

oxide, droperidol, and pentazosine/fentanyl. In contrast, anesthesia in the propofol group was induced with propofol at approx. 2.0 mg/kg, and the only propofol was given until the delivery. After the cord was clamped, fentanyl, remifentanil, and ketamine were only added to propofol for maintenance. Almost all of the patients (99.7%) received total intravenous anesthesia using propofol for maintenance.

Unmatched data analysis

A comparison of the patients' characteristics in the thiopental and propofol groups before matching is given in Table. 1. A significant difference between the two groups was detected in the patients' age, body weight, dose of suxamethonium used, and the proportion of urgent cases, fetal and maternal indication. Regarding the outcomes of the newborns, the APS values at 1 and 5 minutes as well as the proportion of APS<7 at 1 and 5 minutes were similar between the two groups. In contrast, significantly shorter II and ID times were revealed in the thiopental group. The umbilical cord blood pH was significantly higher in the propofol group than in the thiopental group although the proportion of cord blood pH<7.2 was comparable between the two groups (Table. 2).

Regarding the maternal outcomes, the increases in the patients' blood pressure due to tracheal intubation and delivery (i.e. delta BP value) were significantly smaller in the propofol group. The incidences of severe complications such as failed intubation, hypotension, and hypoxia were similar between the two groups. No aspiration was used in either group (Table. 3).

Table 2 The fetal primary and secondary outcomes

	Unmatched, n=911			Matched, n=392		
	Thiopental (n=211)	Propofol (n=700)	p-value	Thiopental (n=196)	Propofol (n=196)	p-value
APS1	7.0 ± 2.1	7.1 ± 2.1	0.64	7.1 ± 2.0	6.6 ± 2.5	0.04
APS1<7 N (%)	57 (27)	154 (22)	0.13	50 (25.5)	61 (31.1)	0.22
APS5	8.4 ± 1.7	8.4 ± 1.7	0.65	8.4 ± 1.7	8.0 ± 2.1	0.16
APS5<7 N (%)	22 (10.4)	61 (8.7)	0.45	20 (10.2)	26 (13.3)	0.35
Cord blood pH	7.28 ± 0.04	7.30 ± 0.05	0.00	7.28 ± 0.04	7.29 ± 0.06	0.13
Cord pH<7.2 N (%)	6 (2.8)	15 (2.1)	0.55	6 (3.1)	6 (3.1)	1.00
N' weight, g	2312.0 ± 763.8	2608.3 ± 661.7	0.00	2334.6 ± 757.7	2316.5 ± 763.0	0.82
II time, min	1.6 ± 1.3	2.2 ± 1.2	0.00	1.6 ± 1.3	2.2 ± 1.4	0.00
ID time, min	5.6 ± 2.0	7.0 ± 2.3	0.00	5.6 ± 2.1	6.5 ± 2.0	0.00

N:number, APS1 or 5: Apgar score at 1 or 5 minutes, N' weight: newborn's weight, ID time: induction-delivery time, II time: Induction-skin incision time

Matched data analysis

The patients' characteristics after matching maternal age, BMI, gestational period, newborn's weight, type of surgery (elective or urgent), pre-eclampsia, and fetal/maternal indication are also summarized in Table.1. With respect to the newborns' outcomes, the APS values at 1 minute was significantly higher (p=0.04) and the II and ID times were significantly shorter (p=0.00) in the thiopental group compared to the propofol group. In contrast, the APS values at 5 minutes, the proportion of APS<7 at 1 and 5 minutes, the umbilical cord blood pH, and the proportion of cord blood pH<7.2 were similar between the two groups (Table. 2).

Regarding maternal outcomes, in the same manner as the unmatched data, the increase in the patients' blood pressure due tracheal intubation or the delivery was significantly smaller in the propofol group. The incidences of failed intubation, aspiration, hypotension, and hypoxia were similar between the two groups (Table. 3).

Discussion

We performed a propensity matching analysis to investigate the outcomes of newborns and women who underwent a cesarean section with general anesthesia, comparing thiopental with propofol induction. Our analyses revealed better well-being of newborns in the early period (i.e., higher APS at 1 min) after birth was found in the thiopental group, probably due to the shorter II and ID time that thiopental provided. In contrast, the other fetal outcomes such as the APS values at 5 minutes, the proportion of APS<7 at 1 and 5 minutes, the umbilical cord blood pH, and the proportion of cord blood pH<7.2 were similar between the two groups. Regarding the mothers' outcomes, compared to thiopental, propofol more effectively inhibited the increase in the maternal blood pressure responding to the tracheal intubation and the delivery.

A 2018 meta-analysis of 13 RCTs[11] showed that there was no significant difference in the APS or umbilical cord blood gas parameters between thiopental and propofol induction. It was also reported that the APS of newborns

Table 3 The Maternal primary and secondary outcomes

	Unmatched, n=911			Matched, n=392		
	Thiopental (n=211)	Propofol (n=700)	p-value	Thiopental (n=196)	Propofol (n=196)	p-value
SBP control, mmHg	130.2 ± 19.6	130.1 ± 20.5	0.65	130.8 ± 19.5	134.6 ± 23.3	0.09
delta SBP, mmHg	26.8 ± 23.0	18.9 ± 21.4	0.00	26.8 ± 23.5	17.6 ± 23.0	0.00
DBP control, mmHg	77.8 ± 13.2	77.2 ± 13.4	0.56	78.0 ± 13.0	79.5 ± 15.3	0.30
delta DBP, mmHg	14.2 ± 15.9	10.2 ± 14.4	0.00	14.2 ± 16.2	9.4 ± 14.7	0.00
HR control, bpm	87.4 ± 20.3	82.6 ± 18.1	0.00	87.1 ± 20.1	84.5 ± 18.7	0.06
delta HR, bpm	14.2 ± 17.8	16.5 ± 18.8	0.10	14.6 ± 17.3	17.2 ± 19.8	0.17
Failed intubation N(%)	0 (0)	3 (0.4)	0.34	0 (0)	2 (1.0)	0.16
Aspiration N(%)	0 (0)	0 (0)	1.0	0 (0)	0 (0)	1.00
Hypotension N(%)	4 (2)	12 (1.9)	0.93	4 (2.1)	1 (0.5)	0.19
Hypoxia N(%)	3 (1.5)	5 (0.8)	0.37	3 (1.6)	2 (1.1)	0.67
Transfusion(%)	3 (1.4)	25 (3.6)	0.28	3 (1.6)	5 (2.6)	0.48
Blood loss, g	911.5 ± 1423.4	1024 ± 621.8	0.10	930.1 ± 1470.2	973.6 ± 637.4	0.71
Fluids, ml	1091.6 ± 363.2	1228.6 ± 593.2	0.00	1098.7 ± 361.5	1153.5 ± 423.4	0.18

N: number, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, delta value= peak value at intubation or at delivery – control value

with propofol and thiopental induction is equally good at 8–9 at 1 min and 9–10 at 5 min[1, 6, 9]. In contrast, we found a significant difference in the early APS (i.e. APS at 1 min) between these two agents, and the APS values were lower than those of reported studies[1, 6, 9] (our study: thiopental, 7.1±2.0 at 1 min, 8.4±1.7 at 5 min, propofol, 6.6±2.5 at 1 min, 8.0±2.1 at 5 min). A possible explanation for this inconsistency is as follows. First, we found that thiopental contributed to higher APS than propofol because thiopental provided shorter induction times (i.e., II and ID time) probably due to the quicker onset time, compared to propofol. We speculate that a quicker delivery affects newborns less because they are exposed to less anesthesia, resulting in higher APS values. Second, >80% of our patients had urgent cesarean sections, whereas those of almost all of the patients in the reported RCTs had elective surgeries. We thus suspect that the well-being of the infants prior to surgery in our series was much worse than that of reported studies.

With respect to maternal outcomes, we observed more stable hemodynamics in the propofol group. These findings are consistent with several RCTs[7, 9-11]. When suppressing the stress response to a nociceptive stimulus, propofol can give patients a higher quality of anesthesia than thiopental. It has also been reported that propofol prevents anesthetic awareness in patients undergoing cesarean section[9]. We thus suggest that propofol is a more suitable anesthetic agent for mothers.

Some limitations of this study should be acknowledged. The first limitation is that the study had a single-center, retrospective design. We thus conducted a propensity score matching analysis for risk adjustment, which ensured a balance between the two groups and eliminated most, but not all, of the potential bias. However, unknown or unmeasured confounders might exist and possibly lead to a residual bias. The possible unknown or unmeasured confounders

in the present study were as follows. First, in accordance with our clinical practice, we used more frequently thiopental in the early study period, and more propofol was used in the late period. Second, we also found a significant difference in the proportion of elective/urgent cases between two groups (elective/urgent, 18.6/81.4% in the thiopental group, 48/52% in the propofol group). We assume that this was probably due to some changes in the obstetric practice. That is, most of elective cesarean section was performed in the city hospital during the early study period. Then, more and more elective surgery is managing in the university hospital after the year 2000. Such these changes in the clinical practice over the years could have influenced the results. The second limitation is that fetal status such as severity of non-reassuring fetal status was unmatched in this study despite matched elective/urgent surgery and fetal/maternal indication. Finally, we evaluated the newborn's outcome using Apgar score and the umbilical cord blood pH, not using long-term neurodevelopmental outcome such as cognitive function in this study. Results of animal experiments strongly suggest that all commonly used anesthetic agents including propofol and thiopental have been shown to cause neurotoxicity and may have an increased risk of poor neurodevelopmental outcome[12, 13]. From this point, the neurodevelopmental performance after birth should've been evaluated as fetal outcome in the present study. However, recent population-based human studies reported a strong evidence for small risk for poor academic or cognitive performance[14, 15]. The international multicenter randomized clinical study investigating neurodevelopmental outcome in infants younger than 60 weeks age receiving general or regional anesthesia did not found an association between brief anesthesia exposure and poor neurodevelopmental outcome[16]. Considering these clinical data, we think that it remains unclear how evidence from basic studies should be interpreted and that there is still no clinical evidence for changing anesthetic strategies in the current clinical practice.

In conclusion, we found that compared with propofol induction, thiopental induction provided better well-being for newborns in the early period after birth, probably due to its quicker onset time. Our results indicate that thiopental affects newborns less because they are exposed to less anesthesia. From this point of view, thiopental might be a favorable choice if the case is urgent for the fetus with a critical condition. However, we found no significant difference in the proportion of the neonatal asphyxia at 1 and 5 minutes after birth. Besides, the other fetal outcome such as APS at 5 min and umbilical cord blood pH were similar. Given these findings, we think that two agents can provide similar fetal outcomes. In contrast, our analyses also indicate that propofol induction can provide better maternal outcomes than thiopental since it can suppress the sympathetic nervous response to a nociceptive stimulus better than thiopental and thus provide a more appropriate depth of anesthesia for women undergoing a cesarean section. Considering the fetal and maternal outcomes of the present study, we suggest that propofol induction may be a first choice for cesarean section with general anesthesia. The present clinical data of a large number of patients with elective and urgent cases reflect real clinical settings and thus provide meaningful information.

Conflict of interest statement: The authors have no conflicts of interest to declare.

Author's contributions: D.O.: Collecting data and writing the first draft of the manuscript. T.K.: Collecting data. J.K.: Collecting data. H.N.: Study design, collecting data, data analysis, and writing the first draft of the manuscript. K.H.:

Supervising the study.

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