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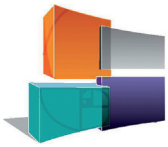

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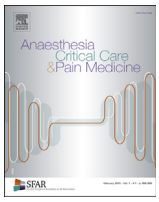

Original Article

Thiopental versus propofol on the outcome of the newborn after caesarean section: An impact study

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SUMMARY

Background: In 2011, the company that produced thiopental in France and in the United States stopped its marketing. Because of limited evidences, the choice of the best induction agent for caesarean section remains controversial, especially in emergency. The objective of this study was to compare the effects of propofol versus thiopental on the Apgar score of the newborn.
Methods: Newborns delivered by elective or emergency caesarean section under general anaesthesia in a university hospital were included from January 2009 to December 2013. Two periods, according to the hypnotic drug used, were compared in this before-and-after comparative study: thiopental before May 2011 and propofol after. The primary outcome was to compare the proportion of newborns with a 5-minute Apgar Score < 7 between both groups.
Results: 367 newborns were enrolled, 178 in thiopental *group* and 189 in *propofol group*. Demographic and clinical characteristics were similar in both groups. The occurrence of a 5-minute Apgar Score less than 7 was not influenced by the use of propofol (OR 1.40 [CI 95% 0.90–2.20] $P = 0.135$). Blood gas analyses and admission's rate in neonatal intensive care unit were similar in both groups.
Conclusions: Thiopental and propofol do not appear to present significant difference in term of outcome of the newborn after caesarean section. In this situation, propofol may probably be a reliable alternative to the supply reduction of thiopental imposed by forces. Prospective studies are required to confirm the safety of propofol, particularly in the long term.

1. Introduction

Nowadays, general anaesthesia for caesarean section is very infrequent compared to regional anaesthesia; therefore, it remains necessary when regional anaesthesia is contraindicated or in case of emergency. The traditional way to perform general anaesthesia for caesarean section was first describe by Hodges and consists in a combination of thiopental and suxamethonium for a rapid sequence induction [1]. This technique has been widely used for decades and remains the gold standard for many physicians experienced in obstetric anaesthesia because of historical reasons, pharmacological properties, license concerns or considerations for the newborn [2]. In May 2011, the company that produced thiopental in France and in the United States stopped manufacturing and marketing it for economical and political reasons [3]. With the cessation of thiopental production, the use of propofol increases in obstetrics. Both propofol and thiopental cross the placental barrier [4], depressing the foetal central nervous system and potentially affect the outcome of the newborn, mainly assessed by the Apgar Score systematically evaluated at 1, 5 and 10 minutes after birth [5]. The 5-minute Apgar Score is acknowledged as the most useful criterion for immediate clinical assessment and care of the newborn, a score equal or greater than 7 being considered normal [6]. Moreover, umbilical cord blood gas assessment also seems to be an objective determination of the foetal metabolic condition at the time of birth [7].

Several old studies [8,9] suggest deleterious effects of propofol on the outcome of the newborn evaluated by the Apgar Score after caesarean section under general anaesthesia. However, these

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studies have small sample sizes and mostly concern elective caesarean sections. Thus, there is a lack of evidence to guide the choice of induction agent in this situation, especially in emergency cases. The objective of this study was to compare the effects of propofol versus thiopental on the proportion of the newborns with an Apgar Score less than 7 after elective or emergency caesarean section.

2. Methods

Ethical approval for this study (Ethical Committee No. 2016 047) was provided by the Ethical Committee in Human Research of University Hospital of Tours, France, on the 22nd of August 2016 and declared to the National Commission for Data Protection and Liberties (CNIL-France). Patients were systematically informed during hospitalisation that their data could be used for scientific purposes. All newborn children delivered by elective or emergent caesarean section under general anaesthesia from the 1st of January 2009 to the 31st of December 2013 in a tertiary obstetric centre were included. Foetal deaths and ASA 4 mothers were excluded. Because of thiopental marketing arrest in May 2011, two groups of patients were compared over the period between 2009 and 2013 in this retrospective before-and-after observational study: – thiopental group for babies born from the 1st of January 2009 to the 30th of April 2011; – propofol group for babies born from the 1st of May 2011 to the 31st of December 2013. Both products came from the same manufacturer during the study period. The primary endpoint was to compare the proportion of newborns with a 5-minute Apgar score below 7 between both groups. The secondary endpoints were to compare the 1 and 10-minutes Apgar scores below 7, the arterial umbilical pH and the admission rate in a neonatal ICU.

2.1. Anaesthetic procedures

Management of general anaesthesia for caesarean section was protocoled according to Hodges' technique during the whole study period and performed by an anaesthetist team comprised of head physician, resident and nurse. Patients did not receive any premedication, except ranitidine systematically given within the hour before surgery. Anaesthesia was induced intravenously by rapid sequence induction, patients in tilt left lateral position, cricoid pressure applied from the beginning of the induction sequence until the trachea was intubated with a cuffed tracheal tube tested for leaks. After a pre-oxygenation with 100% oxygen, either thiopental 5-7 mg kg^{-1} or propofol 2.5–3.5 mg/kg^{-1} were injected, depending on the period – before or after May 2011 -, following by succinylcholine 1 mg/kg^{-1}. Maintenance was performed with inhaled sevoflurane for a target of minimal alveolar concentration at 0.5 to 1 in a 50% nitrous oxide and oxygen mixture. Sufentanil was intravenously added at 0.3 μg/kg^{-1} before cord clamping only in case of pre-eclampsia to avoid laryngoscopy hypertensive peak. The management of postoperative pain was protocolised, patients received systematically intravenous paracetamol 1 g, ketoprofen 50 mg and nefopam 20 g after cord clamping before the end of surgery. The electrocardiograph, heart rate, pulse oximeter, capnograph, bispectral index were displayed continuously, non-invasive blood pressure was recorded every 1 minute. Blood samples were taken immediately after birth from a double-clamped section of the cord and analysed within 10 minutes by Blood Gas Analyzer Radiometer ABL 800®, Brønshøj, Denmark. The examination of the newborn and Apgar scores were assessed at 1, 5 and 10 minutes by a paediatrician and midwife. If necessary, newborns were admitted in neonatal ICU.

2.2. Data

Deliveries between the 1st of January 2009 and the 31st of December 2013 were reviewed from the local birth registry to screen all caesarean sections under general anaesthesia. Data were collected retrospectively consulting anaesthesia paper medical records and obstetrical electronical files by one investigator who was aware of the hypothesis: maternal data were age, height, weight at the day of the anaesthesia consultation, parity, term, medical history, physical status ASA Score; newborn data were date and time of birth, umbilical arterial pH, Apgar Score at 1, 5 and 10 minutes, admission in neonatal ICU; anaesthesia data were causes for general anaesthesia, type and dose of hypnotic drug, indication for caesarean section and Decision-to-Delivery Interval (DDI) for emergency caesarean section, defined as the interval in minutes from the time of decision to carry out the caesarean section to the time of delivery. Levels of urgency were separated into 3 categories based on Lucas' classification [10]: immediate threat to the life of the woman or foetus requiring delivery within 15 minutes (DDI $<$ 15 min); maternal of foetal compromise not immediately life threatening, delivery within 30 minutes (DDI $<$ 30 min); and no maternal or foetal compromise but early delivery needed within 60 minutes (DDI $<$ 60 min).

2.3. Statistical analysis

Data were analysed with R v2.12.1 (Vienna, Austria, 2006). Quantitative data were expressed as mean (± SD) or median (1st–3rd quartiles). Two-tailed Student's *t*-test or Mann-Whitney test were applied to compare quantitative data. Qualitative data were expressed in absolute value (proportion) and compared with a Chi^2 or a Fisher test. Additionally, in the aim to explore confounding factors, a multivariate analysis, using logistic regression, was conducted for Apgar Score at 1, 5 and 10 minutes. The influence of parity (nulliparous vs. multiparous), term of birth, hypnotic type (propofol as the reference vs. thiopental), urgency (divided into 2 groups: urgency $<$ 30 min vs. $<$ 60 min and absence of urgency) and multiple pregnancy on the occurrence of an Apgar Score $<$ 7 at 1, 5 and 10 minutes were tested. The results are expressed in OR and 95% CI. A post-hoc power calculation was performed with a 5% α-risk. A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patients

From the 1st of January 2009 to the 31st of December 2013, 367 of 401 newborns from 382 caesarean sections under general anaesthesia were enrolled, 178 in thiopental group and 189 in propofol group (Fig. 1). Mean doses were 6.0 ± 1.8 mg/kg^{-1} for thiopental and 3.2 ± 0.9 mg kg^{-1} for propofol. The annual rate of caesarean sections was 19 ± 1% in our centre, 10 ± 1% under general anaesthesia. The reasons for a caesarean section were presumed foetal distress (40%), failure to progress in labour (22%), haemorrhage (19%), two and more prior caesarean sections (8%), toxaemia (7%) and maternal history (4%). Lack of time for regional anaesthesia was the primary indication for a general anaesthesia (46%), followed by regional anaesthesia failure (26%) or contraindicated (20%), haemorrhage (4%), refusal (2%) and unknown (2%).

Characteristics of parturients, newborns and anaesthesia management were similar in both groups (Table 1). There was no significant difference between the 2 groups concerning the reasons for a caesarean section and the indications of general anaesthesia ($P = 0.466$ and $P = 0.452$, respectively).

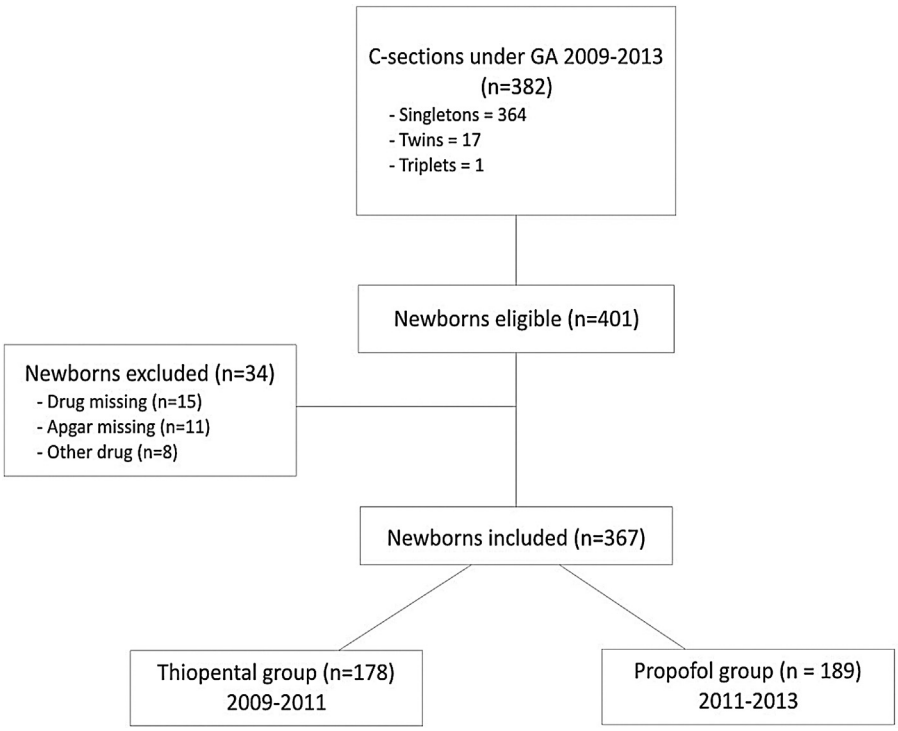

Fig. 1. Flowchart distribution of newborns delivered by caesarean section under general anaesthesia with thiopental or propofol from 2009 to 2013.

Table 1
Characteristics of mothers and newborns receiving thiopental or propofol for caesarean section. Values are mean (SD), median (IQR) or number (proportions).

	Thiopental group (n = 178)	Propofol group (n = 189)	P-value
Mothers			
Age (years)	29.1 ± 5.3	29.3 ± 6.3	0.74
Weight (kg)	77.8 ± 17.8	76.4 ± 14.3	0.43
Height (cm)	162.8 ± 6.4	162.9 ± 7.4	0.96
Nulliparous (n)	79 (44%)	96 (54%)	0.12
ASA physical status	1: 120 (70%)	1: 132 (75%)	0.27
	2: 49 (29%)	2: 45 (25%)	
	3: 2 (1%)	3: 0 (0%)	
Newborns			
Gestational weeks (GW)	37 (32–39)	38 (35–39)	0.16
Preterm birth (< 37 GW)	74 (42%)	74 (39%)	0.64
Moderate [32–37 GW[	37 (21%)	42 (22%)	
Very [28–32 GW[	24 (13%)	19 (10%)	
Extreme < 28 GW	3 (7%)	13 (7%)	
Multiple pregnancies	5 (3%)	12 (7%)	0.09
Pre-eclampsia	11 (6%)	9 (4%)	0.61
Management			
Category of urgency			0.51
None	26 (15%)	34 (18%)	
DDI < 60 min	45 (25%)	36 (19%)	
DDI < 30 min	25 (14%)	27 (14%)	
DDI < 15 min	82 (46%)	90 (48%)	
By night	82 (46%)	85(45%)	1
Dose (mg)	454 ± 127	249 ± 65	-
Dose per kg (mg/kg^{-1})	6.0 ± 1.8	3.2 ± 0.9	-

DDI: decision-to-delivery interval.

3.2. Outcome of the newborn

Regarding the primary endpoint, in the multivariate analysis, the use of propofol compared with thiopental did not increased the risk of the occurrence of an Apgar score below 7 at 5 minute (P = 0.135) but only at 1 min (P = 0.01) (Table 2), confirming the results from the univariate analysis (Table 3).

Regarding the secondary endpoints, there was no statistically significant difference between both groups in the 5-minutes Apgar score below 7 when considering elective or urgent cases (Table 2). Blood gases analyses and admissions rates in neonatal ICU were similar in both groups (Table 2). There was no statistically significant difference between both groups on newborns from pre-eclamptic parturients who received sufentanil before cord clamping (OR 1.29 [CI 95% 0.48–3.62] p = 0.61).

4. Discussion

Our study found no statistically significant difference in the proportion of newborns with a 5-minute Apgar score below 7 when using propofol versus thiopental to induce general anaesthesia for elective and emergent caesarean section. Nevertheless, the proportion of newborns with a 1-minute Apgar score less than 7 was significantly higher in the propofol group. Previous studies suggest that propofol have an important foetal uptake but a short duration of action with high clearance [11], which may have contributed to the rapid recovery at 5 minutes after birth. These results are supported by the measure of umbilical cord blood gases, which is an objective determination of the foetal metabolic condition of the newborn at birth, that shown no difference concerning arterial umbilical pH between both groups.

To our knowledge, among studies comparing thiopental to propofol, our study has the largest population and is the first to deal with elective and emergency caesarean sections. Our findings are consistent with previous studies [8,9] comparing these agents in elective caesarean section. In Capogna's study [9], the number of newborns with a 1-minute Apgar Score < 7 was significantly higher when propofol was used, but similar at 5 minutes. A more recent study [12] showed 57% of newborns with an Apgar Score < 7 in the first minute when propofol was used against 41% with thiopental and no differences at 5 and 10 minutes. There are clear evidences that the 1-minute Apgar Score does not predict infant's outcome for the medium and long term and has no clinical

Table 2
Adjusted Odds Ratio of the impact of the propofol use on the proportion of the newborns with an Apgar score less than 7 after caesarean section on at 1,5 and 10 minutes after birth. Results are expressed as Odds Ratio (95% confidence interval).

	1-min Apgar Score	5-min Apgar Score	10-min Apgar Score
Propofol	2.32 (1.49–3.65) $P = 0.001$	1.40 (0.90–2.20) $P = 0.135$	2.00 (0.99–4.12) $P = 0.053$

Table 3
Results. Values are median (IQR) or number (proportions).

	Thiopental group ($n = 78$)	Propofol group ($n = 189$)	*P*-value
Rate of newborns with an Apgar Score < 7 in all caesarean sections			
1-minute Apgar score	81 (46%)	123 (65%)	0.0002
5-minute Apgar score	58 (33%)	76 (40%)	0.14
10-minute Apgar score	15 (9%)	29 (15%)	0.04
Rate of newborns with a 5-min Apgar Score < 7 in elective or urgent caesarean sections			
Elective	4/26 (15%)	11/34 (32%)	0.23
Urgent :	54/152 (36%)	64/153 (42%)	0.31
DDI < 15 min	29/82 (35%)	42/90 (47%)	0.18
DDI < 30 min	12/25 (48%)	13/27 (48%)	1
DDI < 60 min	13/45 (29%)	9/36 (25%)	0.89
Median arterial umbilical pH and NICU admissions in all caesarean sections			
Arterial umbilical pH	7.28 (7.19-7.32)	7.26 (7.16-7.31)	0.17
pH < 7.00	11 (6%)	15 (7%)	0.55
NICU admission rate	81 (22%)	74 (20%)	0.23

consequence [13]. Contrarily, a low 5-minute Apgar Score confers an increased relative risk of cerebral palsy over that for infants with a score ≥ 7 [14].

In our study, the induction doses of hypnotics appeared to be higher for both thiopental and propofol than in previous studies, respectively 6.0 and 3.2 mg/kg^{-1}. Nevertheless, dosages might be overestimated because the weight was collected on the day of anaesthesia consultation that could take place up to one month before delivery. However, in a prospective study involving 248 patients divided in four groups receiving 4, 5.3, 6.3 and 8 mg/kg^{-1} of thiopental, Apgar scores were not different in the first three groups [15]. Thus, the optimum dose of thiopental for induction is still open for discussion. In the United Kingdom, thiopental is the most commonly used agent to induce general anaesthesia, and a dose of 5–7 mg/kg^{-1} is now recommended [16]. There are no recommendations about propofol for caesarean section, but when considering the equipotency of the two drugs [17], a dose of approximately 3 mg/kg^{-1} seems to be reasonable for young pregnant women.

Several studies have questioned the reliability and validity of the Apgar Score, thus the choice of Apgar Score to measure the primary endpoint could be discussed. At present, the use of this score in clinical routine shows good inter-observer and intra-observer variability [18]. Despite the controversy, The Apgar Score has been used to assess the condition and prognosis of newborn throughout the world for more than 50 years and recent studies confirmed its association with long-term outcome [19].

This study is a retrospective before-and-after trial, which might be source of errors due to confounding and bias, because secular trends or sudden changes make it difficult to attribute observed changes to the intervention. Moreover, it was probably not large enough, with a post-hoc power analyse at 29%, to detect any differences at 5 minutes. Nevertheless, our study has strengths, the Apgar Score was assessed blindly from the hypnotic drug and umbilical cord pH was an objective biologic data. Moreover, during this period, all caesarean sections were screened and few data such as Apgar scores and hypnotic doses were lacking.

Foetal hypoxia is the main cause of neonatal depression besides hypnotic drugs and might have negative effects on the Apgar Score results. In case of foetal hypoxia, the disruption of gaseous exchanges leads to anaerobia, then to acidosis [20,21]. In our study, the mean arterial umbilical pH and severe acidosis occurrences were similar between the two periods, so the incidence of foetal hypoxia was not different in both groups.

Because of the restrictive access and the current higher price of thiopental, propofol is now more and more used for caesarean section under general anaesthesia. Our main results confirm that propofol may be suitable for the newborn, without offering a significant benefit over thiopental for the induction of general anaesthesia for caesarean delivery. Both have advantages and drawbacks: on the one hand, propofol is easier to prepare, with lower risk of administration errors, it may reduce the risk of nausea and vomiting, and is more effective in attenuating the catecholamine response to tracheal intubation. There is no evidence of an increased risk of awareness with propofol. One the other hand, thiopental may be conserved longer because of lower risk for bacterial growth, is painless on administration, and is relatively less vasoplegic than propofol.

According to our results, thiopental and propofol do not appear to present significant difference in term of outcome of the newborn after caesarean section under general anaesthesia. In this situation, propofol may probably be a reliable alternative to the supply shortage of thiopental imposed by forces other than evidence-based practice. However, prospective studies are required to confirm the safety of propofol, particularly on the long term.

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Presentations

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Disclosure of interest

The authors declare that they have no competing interest.

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