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ORIGINAL RESEARCH ARTICLE

# Low-Dose Remifentanil in Preterm Cesarean Section with General Anesthesia: A Randomized Controlled Trial

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## Abstract

**Background and Objective** The conventional technique of general anesthesia induction during a Cesarean section involves the use of opioids only after cord clamping. We hypothesized that the use of remifentanil before cord clamping might reduce the use of maternal supplemental anesthetic agents and improve the maternal hemodynamics status and neonatal adaptation of the preterm neonate.

**Methods** A phase III, double-blind, randomized, placebo-controlled, hospital-based trial enrolled parturients undergoing a Cesarean section under general anesthesia before 37 weeks of gestation. Block randomization allocated pregnant women to remifentanil or placebo. The primary outcome was the rate of newborns with Apgar scores < 7 at 5 min. Secondary outcomes were maternal hemodynamic parameters, complications of anesthetic induction, use of adjuvant anesthetic agents, neonatal respiratory distress, umbilical cord pH, and lactate levels.

**Results** A total of 52/55 participants were analyzed, comprising 27 women in the remifentanil group and 25 in the placebo group. Nine of 27 (33.3%) neonates had an Apgar score < 7 at 5 min in the remifentanil group versus 11/25 (44.0%) in the placebo group ($p = 0.45$, odds ratio = 0.66, 95 confidence interval 0.20–2.18). The blood cord gases, cognitive, behavior, sensory, sleeping, and feeding scores at 1 and 2 years of corrected age were not different. For the mothers, hemodynamic parameters, anesthesia duration, and the cumulative treatment dose until cord clamping did not differ between the groups.

**Conclusions** The use of a low dose of remifentanil before cord clamping for a Cesarean section appears to be safe both for the mother and the preterm newborn, but it does not improve maternal or neonatal outcomes.

**Clinical Trial Registration** ClinicalTrials.gov: NCT02029898.

**Key Points**

The use of opioids before cord clamping for general anesthesia in a preterm Cesarean section is controversial, based on an evaluation of the maternal benefit/neonatal risk balance.

Low-dose remifentanil before cord clamping does not cause overt neonatal respiratory depression at birth and does not improve maternal or neonatal outcomes.

Low-dose remifentanil for general anesthesia before cord clamping may be considered if necessary.

Extended author information available on the last page of the article

## 1 Introduction

Although a Cesarean section (CS) is mostly performed using regional anesthesia, general anesthesia (GA) is required in emergency situations that endanger the life of the mother and/or her fetus, such as placenta abruption, eclampsia, placenta previa with hemorrhage, fetal heart rate abnormalities, or in the case of contraindication or failure of regional anesthesia [1]. In a recent US multi-center cohort, 18% of preterm CSs were performed under GA [2]. The conventional induction of GA during a CS is a modified rapid sequence induction, usually using an anesthetic agent and a rapid-acting muscle relaxant. After cord clamping, opioids are used, and anesthesia is deepened. The use of opioids before cord clamping is controversial, based on an evaluation of the maternal benefit/neonatal risk balance. Indeed, although opioids may reduce maternal sympathetic response, their transplacental passage can induce neonatal respiratory

depression [3], and safety and potential long-term consequences are poorly described [4]. Remifentanil has a rapid onset of action (1–2 min), a short half-life (3–10 min), and a rapid offset of action [5, 6]. Remifentanil crosses the placental barrier with an umbilical venous/maternal arterial ratio from 0.73 to 0.88 [7, 8]. The use of remifentanil during a full-term CS has been evaluated, but never before 37 weeks of gestation [9]. We hypothesized that in GA for a CS before 37 weeks' gestation, the use of low-dose remifentanil prior to cord clamping could reduce the use of adjunctive anesthetic agents, thereby improving the maternal hemodynamic status and neonatal adaptation of the preterm neonate. We aimed to assess the impact of low-dose remifentanil use during GA for a CS on preterm neonates at birth.

## 2 Methods

### 2.1 Study Design

This was a prospective, single-center, phase III, hospital-based, double-blind, randomized, placebo-controlled trial conducted in the tertiary maternity hospital at Rouen University Hospital, France, between September 2014 and June 2018. The study was approved by the Ethics Committee of Rouen, France (Comité de Protection des Personnes Nord-Ouest I, number CPP 01/015/2013) and registered at ClinicalTrials.gov (NCT02029898, EudraCT 2013-001850-83, primary investigator: Fabien Tourrel, date of registration, 8 January, 2014).

### 2.2 Patient Selection

The inclusion criteria were a maternal age more than 18 years, a single pregnancy with an indication for a CS under GA in the context of prematurity (24–37 weeks' gestation), in the context of emergency or not (emergency grade 1 [emergency] to 4 [elective]) [10], and eligibility for social security. Non-inclusion criteria were a maternal disease requiring opioids during induction, severe pre-eclampsia, a 14-week delay between information and actual consent, patients under guardianship, and remifentanil contraindication. Pregnant women were informed during antepartum second trimester pre-anesthetic consultations, an information leaflet was provided to all potential participants, and written consent was obtained by the research team. Parturients were recruited when GA was decided, after screening for the inclusion criteria.

### 2.3 Randomization and Allocation of Treatment

After informed consent, patients were block randomized to remifentanil or placebo by computer generation. The allocation was blind to the participants, the care providers, and the investigator. Only the pharmacy unit was aware of the allocation.

### 2.4 Study Procedures

The anesthetic monitoring included non-invasive measurement of systemic pressure every 2 min and 30 s, as well as continuous electrocardiography and pulse oximetry. Hemodynamic parameters collected in the immediate preoperative period were the reference parameters.

The dose of remifentanil was a 0.5-μg/kg bolus followed by a continuous administration of 0.1 μg/kg/min until hysterotomy. For the remifentanil group, 1 mg of remifentanil was diluted into a volume of 20 mL with saline in a syringe labeled "study drug" (1 mL = 50 μg of remifentanil). For the control group, 20 mL of saline was drawn into an identically labeled syringe. Syringe preparation was performed by a nurse not involved in the patient's care. The visual appearance of remifentanil and the placebo after dilution was identical.

Administration of 0.01 mL/kg of the study drug followed by a continuous infusion of 0.002 mL/kg was performed. After the study drug bolus, 5 mg/kg of thiopental and 1.5 mg/kg of suxamethonium were administered. Study drug administration was stopped before the end of the infusion if there were clinical signs of poor tolerance (hypotension [mean blood pressure less than 45 mmHg], bradycardia [heart rate less than 45 beats per minute], or chest rigidity), or an anaphylactic reaction. The investigator could then unblind the drug. After cord clamping, the anesthetist decides whether to continue the remifentanil infusion or administer sufentanil.

### 2.5 Primary and Secondary Outcomes

The primary outcome measure was the rate of newborns with Apgar scores < 7 at 5 min. Secondary outcome measures were maternal haemodynamic parameters (systolic, diastolic, mean blood pressure, and heart rate), complications of anesthesia induction (difficult intubation defined as a failure after two attempts), use of adjuvant anesthetic agents, neonatal respiratory distress, umbilical cord pH, and lactate levels.

As done during routine care in our center, we collected the following data at corrected ages of 1 and 2 years: weight, height, and head circumference. Cerebral palsy was evaluated according to the European Cerebral Palsy Network definition [11]. Motor development and cognitive function were assessed by a routine score based on the Amiel-Tison and Denver developmental scales [12–14]. The psychosocial behavioral score was defined by items from the French version of the Strengths and Difficulties Questionnaire [15, 16].

### 2.6 Sample Size Calculation and Statistical Analysis

The sample size was based on an expected Apgar score < 7 at 5 min was 40% in the control group. A total of 60 mother-infant dyads (30 per group) was needed to detect a 28% decrease in the Apgar score (based on unpublished local data) with 80% power and a 5% significance level. The rate of neonates with an Apgar score < 7 at 5 min was estimated in each treatment group (remifentanil or placebo) and compared between the two groups using Pearson's Chi-squared test on the intention-to-treat population, i.e., none of the neonates was excluded and the neonates were analyzed according to the randomization scheme. This unadjusted analysis was completed with a logistic regression adjusted on the gestational age at birth ([24–28], [28–32], [32–36]) and the induction time before cord clamping in minutes. Analysis of dichotomous endpoints other than the primary endpoint relied on the same methods, i.e., Pearson's Chi-square test or Fisher's exact test (if necessary) was used to compare observed proportions between groups (e.g., magnesium sulfate [yes/no], hypertension [yes/no], and the sex of the neonate). For quantitative endpoints (e.g., mask ventilation time, insufflation pressure), comparisons between treatment groups relied on the Student's *t*-test or the Mann–Whitney's nonparametric test as appropriate. All statistical tests used the two-sided 0.05 level as their significance threshold. For quantitative variables, means ± standard deviation or medians (first and third quartiles) are reported and for qualitative variables, the frequency and percentages are used.

## 3 Results

Between September 2014 and June 2018, 179 pregnant women who underwent a CS before 37 weeks' gestation were screened for eligibility. Of these, 35 participants did not meet inclusion criteria, 33 were excluded because of an emergency status and 56 declined to participate, leaving 55 women to be randomized. After randomization, one participant no longer needed a CS, one participant withdrew consent before anesthesia, and one patient was determined to be under guardianship. Ultimately, 27 women in the remifentanil group and 25 women in the placebo group were analyzed. Each woman gave birth to a live newborn. Before discharge, two preterm newborns died in the remifentanil group and five died in the placebo group. At 1 year, eight participants dropped out in the remifentanil group, and three in the placebo group. At 2 years, six participants were lost to follow-up in each group (Fig. 1). We found no differences between the groups in terms of the general characteristics, for both the women and the newborns (Table 1).

### 3.1 Primary Outcome

The rate of newborns with an Apgar score < 7 at 5 min was not significantly different between the remifentanil (9/27, 33%) and the placebo (11/25, 44%) groups ($p = 0.49$, adjusted odds ratio 0.66, 95% confidence interval 0.20–2.18).

### 3.2 Secondary Outcomes

#### 3.2.1 Maternal Outcomes

Hemodynamically, the anesthesia procedure was well tolerated in both groups. None of the participants required hemodynamic support with a vasopressor. Only one woman received propofol instead of thiopental to induce anesthesia (remifentanil group). The duration of anesthesia and the cumulative treatment dose until cord clamping did not differ between the studied groups. Induction complications were difficult intubations in two participants in the placebo group. Only one participant (placebo group) required mask ventilation, which the clinician attributed to chest rigidity (Table 2).

#### 3.2.2 Neonatal Outcomes

The blood cord gases were also similar for the two groups. While the use of mask ventilation was similar, the duration of ventilation was longer in the remifentanil group (394 vs 211 s in the placebo group, $p = 0.01$). Similarly, in the case of intubation, the duration of mechanical ventilation was longer in the remifentanil group (29 h vs 17 h in the placebo group), while surfactant administration was similar. Chest compression (4/25, 16%) and epinephrine administration (2/25, 8%) were performed only in the placebo group. Respiratory distress was distributed equally (77.8% in the remifentanil group and 92% in the placebo group, $p = 0.25$). We did not find more chest rigidity in the remifentanil group (28.6% vs 17.4% in the placebo group, $p = 0.48$). Before discharge, two neonates had died in the remifentanil group and five in the control group (7.4% vs 20%, $p = 0.24$) (Table 3).

#### 3.2.3 1-Year and 2-Year Follow-Up

Eleven participants were lost to follow-up at 1 year (eight in the remifentanil group and three in the placebo group), and 12 additional participants at 2 years (six in each group). We did not find any differences in terms of motor, cognitive, behavior, sensory, sleeping, or feeding scores between the groups (Table 4).

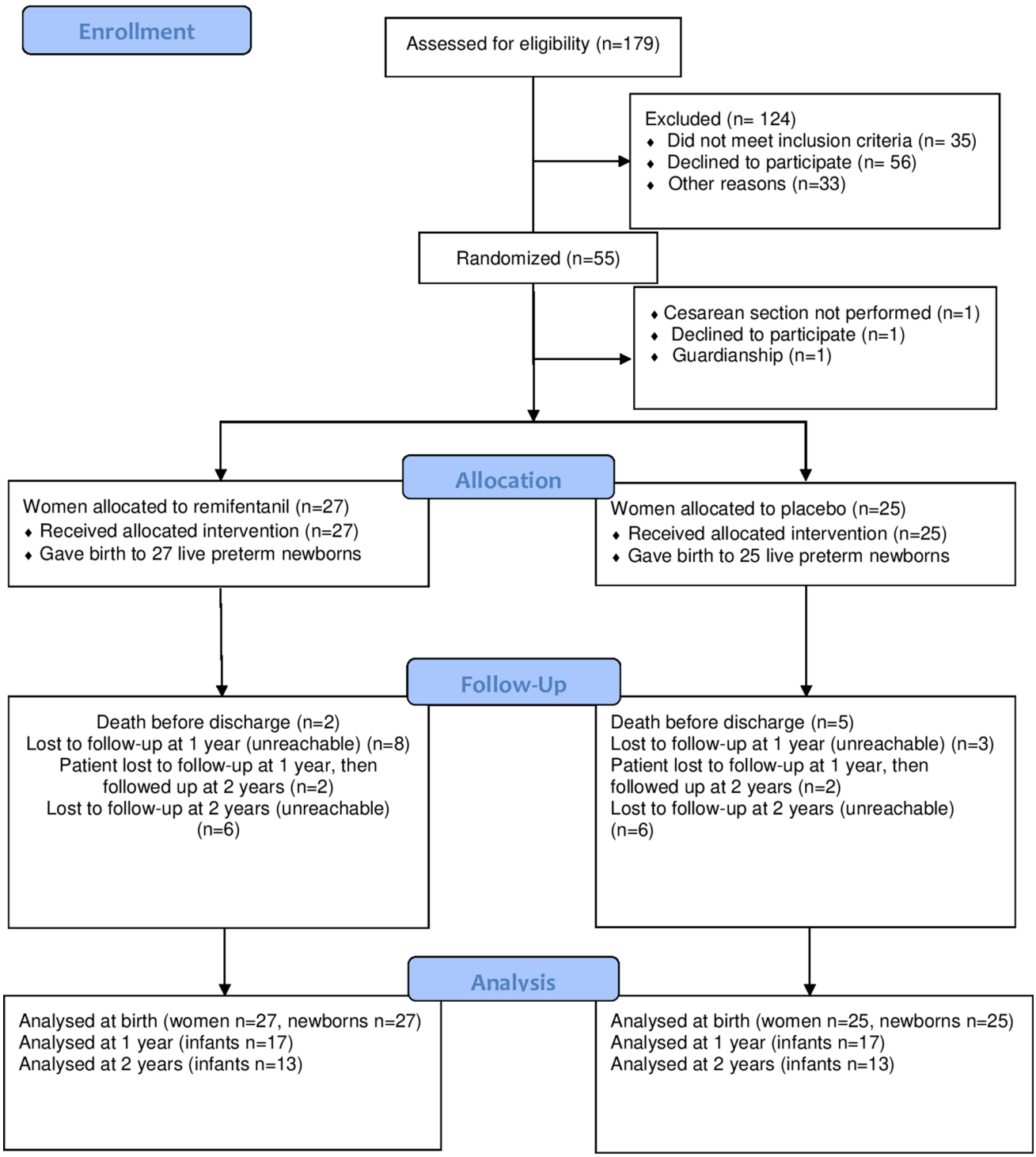


**Fig. 1** Enrollment, randomization, and follow-up of the participants

## 4 Discussion

A low dose of remifentanil during GA before cord clamping in preterm CS did not result in worsening of 5-min Apgar scores compared to placebo, though an increased duration of face mask ventilation at birth was observed in the remifentanil group. Interestingly, we did not find evidence of more chest rigidity after remifentanil exposure. No statistical difference was noted in maternal hemodynamic parameters. Pediatric follow-ups at 1 and 2 years of age did not show any

**Table 1** Patient baseline characteristics

| | Remifentanil group ($n=27$) | Control group ($n=25$) | $p$-value |
|---|---|---|---|
| Mother | | | |
| Age, years | 30.5 ± 6 | 30.9 ± 5.8 | 0.77 |
| Height, cm | 163.8 ± 7.3 | 162.4 ± 7.5 | 0.51 |
| Weight, kg | 74.1 ± 17.9 | 74.6 ± 19.6 | 0.94 |
| BMI, kg/m$^2$ | 27.7 ± 6.7 | 28.2 ± 7.1 | 0.78 |
| Number of delivery | 2.6 ± 1.4 | 2.6 ± 1.8 | 0.79 |
| Cesarean section indication | | | |
| Placental abruption | 4 (14.8) | 5 (20.0) | |
| Bleeding disorders | 1 (3.7) | 1 (4.0) | |
| Placenta previa or accreta | 6 (22.2) | 6 (24.0) | |
| Fetal growth restriction | 3 (11.1) | 1 (4.0) | |
| Fetal heart rhythm anomalies | 5 (18.6) | 4 (16.0) | |
| Other | 8 (29.6) | 8 (32.0) | |
| Emergency category of a cesarean section[a] | | | |
| 1 | 3 (11.1) | 4 (16.0) | |
| 2 | 8 (29.6) | 8 (32.0) | |
| 3 | 6 (22.2) | 5 (20.0) | |
| 4 | 10 (37.1) | 8 (32.0) | |
| Corticosteroids | 17 (63.0) | 16 (64.0) | 0.94 |
| Magnesium sulfate | 11 (40.7) | 9 (36) | 0.73 |
| Newborn | | | |
| Gestational age at birth, weeks | 31.5 ± 3.5 | 31.2 ± 3.9 | 0.73 |
| 24–28 | 9 (33.3) | 6 (24.0) | 0.50 |
| 28–32 | 5 (18.5) | 8 (32.0) | |
| 32–36 | 13 (48.2) | 11 (44.0) | |
| Sex | | | |
| Female | 12 (44.4) | 10 (40.0) | 0.79 |
| Weight, g | 1761 ± 757 | 1712 ± 813 | 0.83 |

Values are mean ± standard deviation or *n* (%)

*BMI* body mass index

[a]Emergency category of a cesarean section defined as follows: 1 Emergency (immediate threat to life of women or fetus); 2 Urgent (maternal or fetal compromise that is not immediately life threatening); 3 Scheduled (needing early delivery but no maternal or fetal compromise); 4 Elective (at a time to suit the woman and/or maternity team (9)

difference in neurosensory outcomes between the remifentanil and placebo groups.

### 4.1 Strengths and Limitations

The main strength of our trial is the randomized, double-blind, controlled design for an emergency procedure. Another strength is that the control group intervention was saline and not another anesthetic agent that could bias the interpretation of the impact of remifentanil.

Our results should be interpreted keeping in mind the limitations of our study. Our study was a single-center investigation that reflects our current local practices. We approached the number of participants to be included without reaching this. Difficulties relating to inclusion were mainly owing to the emergency nature of the CS, despite the information delivered during a pre-anesthetic consultation. The high rate of loss to follow-up at 1 and 2 years of age, and the small number of inclusions clearly limit the interpretation of these results. It should be noted that this study was not designed to show a difference in the long-term neurological outcome, but in neonatal cardiorespiratory adaptation at birth, and that the data at 1 and 2 years were described because they were routinely collected in our center.

### 4.2 Interpretation

General anesthesia for a CS remains challenging, as an acceptable depth of anesthesia needs to be obtained for the parturient with a limited risk for neonates [3]. Traditionally,

**Table 2** Maternal outcomes

| | Remifentanil group $n=27$ | Placebo group $n=25$ | $p$-value |
|---|---|---|---|
| Anesthesia induction procedure | | | |
| Thiopental | 26/27 (96.3) | 25/25 (100) | – |
| Propofol | 1/27 (3.7) | 0 (0) | – |
| Suxamethonium | 27/27 (100) | 25/25 (100) | – |
| Induction time, before cord clamping (min) | 8 ± 5.3 | 7.9 ± 5.4 | 0.94 |
| Cumulative treatment dose administered (µg) | 93 ± 40.5 | NA | – |
| Induction complication | 0 (0) | 2/25 (8) | – |
| Intubation difficulties | 0 (0) | 2/25 (100) | – |
| Mask ventilation[a] | 0 (0) | 1/25 (4) | – |
| If yes, chest rigidity according to the physician | 0 (0) | 1/1 (100) | – |
| Hemodynamic parameters[b] | | | |
| Blood pressure > 15% of reference value | 18/27 (66.7) | 19/25 (76) | 0.55 |
| Systolic blood pressure | 18/18 (100) | 14/19 (73.7) | 0.05 |
| Diastolic blood pressure | 15/18 (83.3) | 19/19 (100) | 0.11 |
| Mean blood pressure | 15/18 (83.3) | 17/19 (89.5) | 0.66 |
| Blood pressure < 15% of reference value | 7/27 (25.9) | 4/25 (16) | 0.50 |
| Systolic blood pressure | 3/7 (42.9) | 2/4 (50) | – |
| Diastolic blood pressure | 7/7 (100) | 4/4 (100) | – |
| Mean blood pressure | 5/7 (71.4) | 3/4 (75) | – |
| Heart rate > 20% of reference value | 12/27 (44.4) | 12/25 (48) | 1.00 |
| Bradycardia (< 45 beats per minute) | 3/27 (11.1) | 2/25 (8) | 1.00 |
| Anesthesia procedure after cord clamping | | | |
| Use of maintenance drug (excluding opioids) | 14/27 (51.9) | 11/25 (44) | 0.59 |
| Thiopental | 6/27 (22.2) | 6/25 (24) | – |
| Propofol | 1/27 (3.7) | 1/25 (4) | – |
| Ketamine | 3/27 (11.1) | 0 (0) | – |
| Sevoflurane | 7/27 (25.9) | 5/25 (20) | – |
| Isoflurane | 0 (0) | 0 (0) | – |
| Nitrous oxide | 0 (0) | 1/25 (4) | – |
| Atracurium | 4/27 (14.8) | 1/25 (4) | – |
| Cisatracurium | 2/27 (7.4) | 1/25 (4) | – |
| Celocurine | 2/27 (7.4) | 2/25 (8) | – |
| Use of opioids | 27/27 (100) | 25/25 (100) | |
| Sufentanil | 14/27 (53.8) | 10/25 (40) | 0.40 |
| Remifentanil | 13/27 (48.1) | 15/25 (60) | |

Values are $n$ (%), $n$ = patients with change in hemodynamic parameters

*NA* not applicable

[a]Mask ventilation in the case of ventilation difficulties after induction

[b]Hemodynamic parameters collected in the immediate preoperative period were the reference parameters

opioids have been used only after cord clamping to avoid neonatal respiratory depression. It remains a matter of debate, and the use of opioids before cord clamping without any neonatal side effects could be a feasible alternative. For parturients, the addition of opioids potentially improves the depth of anesthesia [17] and prevents hypertension at intubation, especially in pre-eclampsia [18, 19]. We did not find an impact of remifentanil on maternal hemodynamic parameters. The absence of a preventive effect on the pressor response to laryngoscopy, compared with other studies that showed a pressor preventive effect of remifentanil [17], may be explained by the low dose used to prevent potential adverse neonatal respiratory effects, and the non-inclusion of parturients with pre-eclampsia. We chose not to include patients with severe pre-eclampsia because there was strong evidence that remifentanil controlled post-intubation blood

**Table 3** Neonatal outcomes

| | Remifentanil group $n=27$ | Placebo group $n=25$ | $p$-value |
|---|---|---|---|
| Apgar score | $n=27$ | $n=25$ | |
| Apgar 1 min | 5 [2; 8] | 4 [2; 8] | 0.53 |
| Apgar 1 min < 7 | 16 (59.3) | 15 (60.0) | 0.96 |
| Apgar 10 min | 10 [8; 10] | 9 [8; 10] | 0.31 |
| Apgar 10 min < 7 | 2 (7.4) | 2 (8.0) | 1.00 |
| Cord blood sample | $n=25$ | $n=21$ | |
| pH | 7.2 ± 0.2 | 7.2 ± 0.1 | 0.68 |
| Lactate, mmol/L | 4.5 ± 5.3 | 4.6 ± 4.4 | 0.64 |
| Bradycardia (< 100 beats per minute) | 9 (33.3) | 10 (40) | 0.77 |
| Chest compression | 0 (0) | 4 (16) | 0.05 |
| Epinephrine | 0 (0) | 2 (8) | – |
| Respiratory distress[a] | 21 (77.8) | 23 (92) | 0.25 |
| If yes, chest rigidity | 6 (28.6) | 4 (17.4) | 0.48 |
| Mask ventilation | 21 (100) | 22 (95.7) | – |
| Mask ventilation time, s | 393.9 ± 273.8 | 211.1 ± 170.9 | 0.01 |
| Insufflation pressure, $H_2O$cm | 21.3 ± 3.6 | 19 ± 5.8 | 0.13 |
| Intubation | 7 (33.3) | 9 (39.1) | 0.76 |
| Duration of mechanical ventilation, h | 29.3 ± 29.5 | 17.4 ± 14.1 | – |
| Surfactant administration | 5 (71.4) | 6 (66.7) | – |
| Death at discharge | 2 (7.4) | 5 (20.0) | 0.24 |

Values are means ± standard deviation or *n* (%)

[a]Respiratory distress was defined by tachypnea > 60/min or apnea < 20/min or respiratory severity score > 4/10 (16)

pressure compared with placebo [19–21]. Since 2020, the Société Française d'Anesthésie et de Réanimation has recommended that patients with severe pre-eclampsia undergoing GA receive an injection of morphine during the induction to limit the hemodynamic consequences of tracheal intubation [22]. At the time the protocol was written, these practices were already in place in the department, and it did not seem ethical for a patient with severe pre-eclampsia not to receive an opioid if she was in the placebo group. We hypothesize that the antihypertensive beneficial effect of remifentanil is more readily demonstrated in patients with pre-eclampsia, who exhibit higher blood pressure. Finally, a low dose of remifentanil did not change the anesthesia procedure and appears to be safe for the parturient. Two randomized controlled trials with 40 and 50 women found that remifentanil for GA for a term CS was as safe as saline and dexmedetomidine, respectively [8, 23]. This reassuring evidence is also supported by a meta-analysis about induction opioids for a CS [24].

Given the high placental transfer of remifentanil, respiratory depression and chest rigidity are concerns at birth. In a randomized controlled trial with 40 parturients, two term newborns exposed in utero to remifentanil required naloxone and were admitted to the neonatal intensive care unit for observation [8]. Draisci et al. demonstrated that newborns in the remifentanil group had lower 1-min and 5-min Apgar scores, but still above 8 at 5 min [25]. A recent meta-analysis did not show any evidence of a deleterious impact of remifentanil on cardiorespiratory adaptation [24]. To our knowledge, there have been no studies to date showing a deleterious effect of remifentanil on newborns at birth [17, 26–29].

At birth, neonatal outcomes were broadly similar between the remifentanil and placebo groups. In the case of intubation, the duration of mechanical ventilation was longer in the remifentanil group, while surfactant administration was similar. Given the pharmacokinetic properties of remifentanil, it seems unlikely that the increase in ventilation time was related to remifentanil exposure. Antenatal remifentanil exposure did not change the cord pH and lactate levels, suggesting no adverse impact on fetus vitality.

Interestingly, we did not find that remifentanil had any impact on the occurrence of chest rigidity. Furthermore, we noted chest rigidity in 4/25 patients in the placebo group (16%). This misdiagnosis could be partly explained by the difficulty in differentiating chest rigidity from other causes of neonatal respiratory distress. However, the participants in the remifentanil group had a longer duration of mask ventilation (394 ± 274 s vs 211 ± 171 s in the control group, $p=0.01$), without other respiratory morbidities. The absence

**Table 4** 1-Year and 2-year follow-up

| | 1-Year follow-up | | | 2-Year follow-up | | |
|---|---|---|---|---|---|---|
| | Remifentanil group $n=17$ | Placebo group $n=17$ | *p*-value | Remifentanil group $n=13$ | Placebo group $n=13$ | *p*-value |
| Weight, kg | 8.9 ± 0.8 | 8.4 ± 1.4 ($n=16$) | 0.20 | 11.2 ± 1.8 | 10.6 ± 2.6 | 0.53 |
| Height, cm | 72 ± 2.9 | 72.5 ± 4.2 ($n=15$) | 0.67 | 85.2 ± 3.6 | 83.2 ± 5.6 | 0.24 |
| BMI, kg/m$^2$ | 17.3 ± 1.3 | 15.9 ± 1.2 ($n=15$) | 0.01 | 15.4 ± 1.4 | 15.1 ± 2 | 0.98 |
| Head circumference, cm | 45.9 ± 1.5 | 45.3 ± 1.9 ($n=16$) | 0.30 | 48.2 ± 1.5 | 52.1 ± 14.4 | 0.48 |
| Motor score | | | | | | |
| Score 1 (=normal) | 14 (82.4) | 14 (82.3) | NA | 13 (100) | 9 (69.2) | NA |
| Score 2 | 0 (0) | 2 (11.8) | | 0 (0) | 3 (23.1) | |
| Score 3 | 3 (17.6) | 1 (5.9) | | 0 | 0 | |
| Cerebral palsy | 2 (11.8) | 0 (0) | NA | 0 (0) | 0 (0) | NA |
| Cognitive score | | | | | | |
| Score 1 (=normal) | 12 (70.6) | 11 (64.7) | NA | 11 (84.6) | 6 (46.1) | NA |
| Score 2 | 4 (23.5) | 5 (29.4) | | 2 (15.4) | 5 (38.5) | |
| Score 3 | 1 (5.9) | 1 (5.9) | | 0 (0) | 1 (7.7) | |
| Score 4 | 0 (0) | 0 (0) | | 0 (0) | 1 (7.7) | |
| Behavior score | | | | | | |
| Score 1 (=normal) | 14 (87.4) | 14 (82.2) | NA | 10 (76.9) | 8 (61.5) | NA |
| Score 2 | 1 (6.3) | 0 (0) | | 2 (15.4) | 2 (15.4) | |
| Score 3 | 1 (6.3) | 2 (11.8) | | 1 (7.7) | 1 (7.7) | |
| Score 4 | 0 (0) | 1 (5.9) | | 0 (0) | 1 (7.7) | |
| Epilepsy treatment | 1 (5.9) | 0 (0) | NA | 0 (0) | 0 (0) | |
| Visual score | | | | | | |
| Score 1 (=normal) | 16 (94.1) | 14 (82.3) | NA | 12 (92.3) | 12 (92.3) | NA |
| Score 2 | 1 (5.9) | 2 (11.8) | | 1 (7.7) | 1 (7.7) | |
| Score 3 | 0 (0) | 1 (5.9) | | 0 (0) | 0 (0) | |
| Normal auditive score | 17 (100) | 17 (100) | NA | 13 (100) | 13 (100) | NA |
| Sleeping score | | | | | | |
| Score 1 (=normal) | 17 (100) | 13 (76.4) | NA | 12 (92.3) | 11 (84.6) | NA |
| Score 2 | 0 (0) | 2 (11.8) | | 1 (7.7) | 2 (15.4) | |
| Score 3 | 0 (0) | 2 (11.8) | | 0 (0) | 0 (0) | |
| Feeding score | | | | | | |
| Score 1 (=normal) | 17 (100) | 14 (82.3) | NA | 11 (84.6) | 11 (84.6) | NA |
| Score 2 | 0 (0) | 2 (11.8) | | 1 (7.7) | 1 (7.7) | |
| Score 3 | 0 (0) | 1 (5.9) | | 1 (7.7) | 1 (7.7) | |

Values are means ± standard deviation or *n* (%)

*BMI* body mass index, *NA* not applicable

**1-Year follow-up: Motor score:** Score 1: Sitting up: holds himself well, starts to do the "little rabbit" position. Small delay in acquisitions but no tonus abnormality on examination. Stereotypically moves his hand towards the object before catching it. Score 2: Sits up alone, sits upright. Four-legged, stands, walks held. Orientation of grasp, puts hand in proper position to grasp a ruler. Score 3: Turns around, crawls. Sits up: holds for a while with kyphosis of the axis. Distal hypertonia of the lower limbs. Unilateral deficit. Ulnar-palmar grasping of objects. **Cognitive score:** Score 1: Pinches thumb index finger. Explores objects carefully and brings little to mouth. Begins to put an object in a box. Understands simple commands, says 2–3 words, understands prohibition. Search for toy hidden ostensibly under a cloth. Score 2: Less elaborate exploratory activities, puts a lot in mouth. Empty boxes and throw away. Stares at stranger, doubles monosyllables. Points, waves goodbye, and cheers. Coat sign (anticipation of situations). Score 3: Good eye contact but non-functional explorations. Moderate babbling without dissyllables. In front of an object at a distance, only looks at it

Score 4: Poor contact. Stereotyped manipulations or no manipulations. Does not respond to the mother's suggestions. **Behavior score:** Score 1: Mo problem. Score 2: Demanding child, easily calmed down. Score 3: Passive or restless child, requiring intervention of the entourage. Score 4: Agitated child, difficult to console or extremely passive. **Visual score:** Score 1: Visual pursuit over 180° with parallelism of the eyeballs. Score 2: Strabismus with good fixation of each eye and good pursuit, myopia. Score 3: Strabismus with poor fixation of one eye, disturbed pursuit. **Sleep score:** Score 1: No problem. Score 2: Small difficulties easily solved. Score 3: Medium difficulties requiring special attention from parents to manage the problem. **Feeding score:** Score 1: No problem. Score 2: Small difficulties easily solved. Score 3: Moderate difficulties requiring

**Table 4** (continued)

special attention from parents to manage the problem

**2-Year follow-up: Motor score:** Score 1: Runs, climbs stairs, jumps on both feet. Protected falls when running. Starts scribbling on his/her own or by invitation. Stacks at least 2 cubes. Score 2: Walks after 18 months. Unprotected falls. Approaches object directly, picks up crumbs. **Cognitive score:** Score 1: Fits in with thought and application (puzzle). Wants to dress himself. Can pretend to make a phone call (with or without phone). Names on picture, puts 2 words together. Playing identification games with dolls or stuffed animals. Seeks to share attention and exchange. Score 2: Identifies object or animal on picture without naming them. Identifies body parts. Attention more labile, gets bored fairly quickly. Random embeddings. No identification games. Uses isolated words, accepts to repeat them. Score 3: No preference for an object or activity. Only moves, empties and throws away, does not put back in box. Gibberish without understandable words. Does not know how to express his/her desire by gesture or attitude. Score 4: Very stereotyped activities. Does not point, does not follow gaze. Production of stereotyped sounds. Self or hetero aggressive. **Behavior score:** Score 1: No problem. Score 2: Demanding child, easily calmed down. Score 3: Passive or fidgety child, requiring intervention from the entourage. Score 4: Agitated child, difficult to console or extremely passive. **Visual score:** Score 1: 180° visual tracking with parallelism of the eyeballs. Score 2: Strabismus with good fixation of each eye and good tracking, myopia. **Sleep score:** Score 1: No problem. Score 2: Small difficulties easily solved. **Feeding score:** Score 1: No problem. Score 2: Small difficulties easily solved. Score 3: Moderate difficulties requiring special attention from parents to manage the problem

of a difference in neonatal adaptation is of paramount importance as GA was most often indicated in vulnerable critical situations at a high risk of asphyxia at birth, neonatal mortality, morbidity, or long-term neurodisability [30].

The results of the follow-up at 1 and 2 years did not show any difference in terms of growth and neurosensory outcomes. However, this study cannot conclude because of the high rate of lost to follow-up at 1 and 2 years and the modest number of inclusions. Nevertheless, in a murine model with intracortical injections of ibotenate, remifentanil exerted a beneficial effect against excitotoxicity associated with a reduction in the brain lesion and prevention of some behavioral impairments [31]. In humans, this potential neuroprotective effect could be of interest, as GA is performed in emergency situations that increase the risk of neurodevelopmental sequels in preterm infants, but a larger multi-center randomized study is needed.

## 5 Conclusions

A low dose of remifentanil before cord clamping during GA in preterm CS does not cause overt neonatal respiratory depression at birth. Further studies are needed to assess the clinical effect of remifentanil on long-term neurodevelopmental outcomes in infants.

## Declarations

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**Conflict of Interest** Clément Chollat, Fabien Tourrel, Estelle Houivet, Romain Gillet, Eric Verspyck, Maryline Lecointre, Stéphane Marret, and Vincent Compère have no conflicts of interest that are directly relevant to the content of this article.

**Ethics Approval** This study protocol was reviewed and approved by the Ethics Committee of Rouen, France (Comité de Protection des Personnes Nord-Ouest I, approval number 01/015/2013) and registered at ClinicalTrials.gov (NCT02029898, EudraCT 2013-001850-83, primary investigator: Fabien Tourrel, date of registration, 8 January, 2014).

**Consent to Participate** Written informed consent was obtained from the participants by the research team before randomization.

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

**Code Availability** Not applicable.

**Author Contributions** CC and FT conceptualized and designed the study, coordinated and supervised the intervention, collected the data, and participated in manuscript writing and editing. EH carried out the power analyses and participated in manuscript editing. SM and RG participated in the project conception, data management, manuscript writing, and editing. EV participated in manuscript writing and editing. ML participated in the data collection, data management, and manuscript editing. VC analyzed and interpreted the data and participated in manuscript editing.

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