Premedication Trial for Tracheal Intubation of the NEOnate (PRETTINEO)

A multicenter double blind randomized controlled trial comparing "atropine+propofol" vs "atropine+atracurium+sufentanil" as a premedication prior to endotracheal intubation of the neonate– *English Version (translated from the original French version)*

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Scientific justification and general description of the research

Name and description of the experimental drug(s)

Propofol (2,6-diisopropylphenol) is a diisopropylphenol belonging to the class of general anesthetics. Anesthetic properties are likely mediated by depression of NMDA receptor neuro-excitatory activity and activation of GABA A receptors [1].

Atropine is a parasympatholytic used in pre-anesthesia as a protection against vagal manifestations.

Sufentanil is a rapid, short-acting synthetic morphine used in anesthesia and resuscitation.

Atracurium is a non-depolarizing, short-acting, fast-acting neuromuscular blocker used to facilitate tracheal intubation and artificial ventilation.

Scientific data from the literature

Prevention of pain in newborns should be a priority for all caregivers, as pain transmission pathways are present in the fetus as early as 22 weeks of gestation[2]. The management of newborn pain by pharmacological or non-pharmacological means was the subject of a consensus by the American Academy of Pediatrics and the Canadian Pediatric Society in 2000 [3]. A large observational study conducted in the Paris region in 2005-2006 reports that the median number of painful procedures in neonatal intensive care units is 16 per child per day of hospitalization [4]. Beyond its ethically obvious nature, the management of newborn pain is important at many levels. Repeated exposure to pain during the neonatal period has adverse consequences on brain development[5]. In the long term, we observe in the former very premature infants an alteration of the sensitivity to the pain (which persists at least until the adolescence) [6] and behaviorial modifications (anticipatory fear for pain with reactions of withdrawal) [7]. Premature newborns who have the highest risk of having neurological sequelae are also those who experience the most painful stimulation during their stay in neonatal resuscitation [8]. Finally, pain contributes to parental stress, which is all the more important because separation is early and prolonged [9].

Endotracheal intubation is commonly performed in the NICU and delivery room. A declarative survey conducted in France in 46 NICUS and 38 delivery rooms showed that only 74% of newborns were intubated with sedation and / or analgesia [10]. A posteriori analysis of the EPIPPAIN study showed that in 12 out of 13 pediatric and neonatal ICUs in Ile de France, specific premedication was only administered in 56% of neonatal intubations [11]. Yet this procedure is a painful and unpleasant experience [12,13] and there is a definite interest in intubating with premedication, as recently recommended by the American Academy of Pediatrics (AAP) [14]. Premedication reduces the time and number of attempts necessary for intubation [15]. Intubation

without analgesia increases intracranial pressure and thus potentially increases the risk of intraventricular hemorrhage [16]. In addition, laryngoscopy deforms the larynx and upper airways causing activation of the sympathetic and parasympathetic system responsible for bradycardia and increased intra-thoracic pressure [17].

Reasons for not using analgesia may include lack of familiarity with premedication, fear of adverse effects, lack of sufficient evidence of efficacy, or lack of consensus on the optimal regimen of premedication. Several therapeutic classes have been evaluated for premedication before intubation and have been the subject of a recent comprehensive review [18]. Barbiturates do not diminish the occurrence of desaturations [17,19]. Midazolam seems dangerous if used alone [20]. Opioids used without a neuromuscular blockerare associated with frequent desaturations [21,22]. On the other hand, the combination of opioid and a neuromuscular blocker improves the conditions of intubation [22]. This opioid+neuromuscular blocker combination is therefore considered the gold standard of premedication before intubation [23].

Propofol is a diisopropylphenol which has many theoretical advantages. Its activity is observed in less than a minute after intravenous administration. The duration of action is brief, the half-life in adults is 1.8 to 4.1 minutes [24]. The preparation of this drug is fast and easy because it is not necessary to dilute it, which decreases the risk of error. This drugcan be used alone because it has no vagolytic action. It decreases the pharyngeal reflex and muscle tone facilitating intubation [25] and allows the maintenance of spontaneous breathing. Although it is not an analgesic, its effectiveness has been proven in many studies in children. It is commonly used as a premedication for bronchial [26]or digestive [27]fibroscopy in children. Propofol has also been shown to be effective for difficult intubations, for intubation in patients with vigil coma and for insertion of laryngeal and pharyngeal masks[28,29].

The use of propofol is common in adults and children, in intensive care and anesthesia. Reported adverse reactions of propofol are mild injection pain and systemic hypotension. From a hemodynamic point of view, propofol decreases cardiac pre-load and post-load that can lead to systemic hypotension due to a decrease in sympathetic tone and vascular resistance[30] without any change in myocardial contractility[31]. In most cases, hypotension is brief without requiring volume expansion [32]. In the respiratory system, it has been shown that propofol can reduce the diameter of the airways; this effect is completely reversible with continuous positive airway ventilation [33]. In less than 2% of children undergoing endoscopy of the upper airway spontaneous ventilation under propofol, spontaneously resolving episodes of desaturation have been reported [34]. Only continuous intravenous infusion of propofol at a dose greater than 5mg / kg / h has been associated in adults and children with severe complications associating zinc deficiency, metabolic acidosis, rhabdomyolysis, hyperkalemia and renal failure that may lead to deaths [35]. Finally, maternal anesthesia with propofol for caesarean sections does not significantly alter the Apgar score in neonates compared to other analgesic protocols [36,37].

Several animal studies have been conducted on the possible neurotoxicity of propofol. Indeed, propofol positively modulates the inhibitory function of GABA (gamma-amino-butyric acid)neurotransmitters causing a GABA accumulation by inhibition of reuptake and is an NMDA (N methyl D aspartate) receptor antagonist. In murine models, NMDA antagonists can induce massive neurodegeneration by apoptosis [38]. However, these events are dependent on the dose administered, the chosen injection schedule (single dose or continuous infusion), the duration of exposure, stage of development and other anesthetic agents administered simultaneously[39]. Al-Jadhari *et al.* in a dose-response study showed that exposure of neuronal growth cones from chicken embryos resulted in collapse of these embryos, which was reversible if the dose used was low and the exposure time was short[39]. The toxic doses used in this study are much higher than the doses used in humans. Vutskits *et al* identified an impairment of dendritic growth of rat neurons in vitro at doses considered clinically relevant [40]. In contrast, propofol has beneficial effects described by its antioxidant properties in the adult animal where a model of cerebral ischemia-reperfusion is observed to decrease neuronal apoptosis [41]. The mechanism of action involves a decrease in lipid peroxidation [42]and a decrease in the amount of free radicals [43]. In animals, propofol also has immunomodulatory effects. There is a decrease in mortality in anesthetized rats after induction of septic shock by bacterial endotoxin [44]. Propofol decreases the synthesis of pro-inflammatory cytokines (TNFα and IL-6) in vivo and in vitro [45]. It alters the immune functions of monocytes and polymorphonuclear neutrophils [46]. It has a protective effect on the lungs after experimental induction of ARDS with oleic acid [47].

The interpretation of such experimental results is delicate and experts recommend the utmost caution in the transposition of animal data to humans [48]. All families of anesthetic drugs (opioids, benzodiazepines, GABA agonists, NMDA antagonists) have been implicated in the development of brain development disorders [48,49]. However, the fight against pain must remain a priority in Neonatology while ensuring a rigorous and long-term evaluation of new practices.

Researchers in San Diego and Dartmouth have previously studied the value of adding a fast-acting neuromuscular blocker to an opioid before intubation in an open randomized study [22]. The atropine-fentanyl combination was compared to the atropine-fentanyl-mivacurium combination. The results of this study showed that the use of neuromuscular blocker combined with analgesia and anti-cholinergic decreased the time and number of attempts needed to intubate (confirmation of the secondary hypothesis) without significantly decreasing episodes of saturation lower than 75% (reversal of the main hypothesis). In the mivacurium group (n = 21, mean weight: 1560g, mean age adjusted 31SA), 29% of children experienced a desaturation episode <75% with a duration greater than 30s. The total duration of the procedure was 31% shorter in the group receiving neuromuscular blocker and the total duration of laryngoscopy decreased by 41%.

Créteil's team carried out a prospective study for the evaluation of premedication with atropine, sufentanil and atracurium in newborns with less than 32 SA and / or less than 1500g (n =

35 intubations, median birth weight: 850g, mean gestational age at birth: 27.6 weeks, median age at intubation: 10 days, (IQR [4-16]) [50].The intubation conditions reported by the operator were "good or excellent" in 94% of cases and the success rate at the first attempt of 75%. However, desaturations below 80% lasting at least one minute were observed in one out of two cases. Episodes of desaturation are therefore a common adverse event in this population during the intubation procedure with the atropine-opioid-neuromuscular blocker combination. The time required to prepare drugs is another disadvantage of this triple therapy since Ghanta *et al.* reported a preparation time of 960 seconds (900 to 1200s) [51]. It is necessary to dilute the three products, each dilution exposing to a risk of error. Other notable adverse effects include the induction of thoracic rigidity or laryngospasm by fentanyl and its derivatives, making mechanical ventilation or intubation more difficult [52]. The neuromuscular blockers, in turn, induce prolonged muscle relaxation and apnea requiring rapid initiation of assisted ventilation. But they do not always prevent the occurrence of chest blocking phenomena induced by sufentanil [50]. These two phenomena can contribute to the occurrence of episodes of prolonged and/or severe desaturation.

In neonates, the only prospective randomized trial evaluating propofol as premedication before intubation was performed in an Australian center [51]. The hypothesis was that by allowing spontaneous breathing, the propofol-treated group would have fewer apneas and therefore potentially fewer episodes of hypoxemia during the procedure. The authors compared propofol at a dose of 2.5 mg / kg renewable as needed (n = 33) to a morphine-atropine-suxamethonium combination (n = 30) in neonates born at 25 to 31 weeks of gestation, with birth weights ranging from 759 to 1612g, intubation weight from 810 to 1972g, and age at intubation from 1 to 33 days. The results showed that sufficient muscle relaxation or sleep was achieved in 60 seconds in each group and that the intubation time was significantly shorter in the "propofol" group (120s versus 260s). No difference in blood pressure and heart rate was observed between the groups. The median minimum oxygen saturation values during the procedure were significantly lower in the "morphine-atropine-suxamethonium" group (60 versus 80%). However, this minimum single saturation value does not necessarily indicate the duration or severity of hypoxia. The onset of anesthesia was faster in the "propofol" group (780 vs 1425s) and no serious adverse events were observed during the study, including no grade III or IV intraventricular hemorrhage.

Other descriptive studies have been published on the use of propofol as premedication before neonatal intubation. Papoff *et al.* reported the use of fentanyl (1.5 µg / kg in 1 minute) and propofol (2 mg / kg in 20 seconds) in 21 term or near term neonates [53]. The intubation conditions were good despite the occurrence of abrupt desaturations (> 60%) in 7 cases. In the majority of these cases, these desaturations were accompanied by a drop in blood pressure (undefined) that the authors treated with the administration of 10 ml / kg of normal saline bolus. In conclusion, the authors considered this association as safe and effective.

More recently, Welzing et al. published a pilot study of 13 newborns less than 8 hours of life eligible for the INSURE procedure (INtubation SURfactant Extubation) [54]. This pilot study was

prematurely interrupted due to the frequency of arterial hypotension defined by a mean arterial blood pressure <25 mm Hg. Propofol was administered as a bolus dose of 1 mg / kg in the first 6 patients and over 60 seconds in the 7 following. In the first phase (bolus), 3 out of 6 patients experienced hypotension <25 mmHg 10 minutes after administration. In the second phase (1-minute injection), two patients experienced hypotension <25 mm Hg. In these 7 infants, mean pressure decreased from 37 mmHg to 28 mmHg 5 minutes after propofol administration. No significant changes in heart rate and O2 saturation were observed. No complications such as intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, retinopathy or bronchopulmonary dysplasia were observed in the 13 children who participated in the study. 85% of intubations were performed under conditions deemed "good" or "excellent".

In 2013, Simons *et al.* published their experience with propofol in 62 neonatal intubations [55]. The initial dose of 2 mg / kg was sufficient for 37% of patients. Hypotension occurred in 39% and was more common in the first day of life. However, the diversity of associated pathologies (necrotizing enterocolitis, sepsis) could potentially have increased the risk of hypotension.

Between March 2007 and December 2008, the NICU at the Centre Hospitalier Intercommunal de Creteil conducted an observational study of 33 intubations with propofol in infantsborn after 32 weeks of gestation[56]. The dose of 2.5 mg / kg was administered over 60 seconds and could be repeated if necessary. Intubation conditions were rated as "good" or "excellent" in 91% of cases. Desaturation <80% for at least 1 minute occurred in 17 cases (52%) and bradycardia <100 / min for at least 1 minute in 5 cases (15%). Mean arterial blood pressure decreased at 5 and 10 minutes after injection (respectively -6.6 and -9.9 mmHg) but normalized spontaneously 15 minutes after injection. No significant changes in heart rate were observed. The identified risk factors for onset of desaturation were lower pre-intubation SpO2 (93% vs 98%) and longer duration of intubation (394 sec vs 167 sec).

Predictable benefits and risks known to patients who are eligible for research

The expected benefit for infants participating in this study is the systematic administration of a premedication before tracheal intubation except forlife-threatening situations. These infants will also benefit from sustained surveillance during and after the procedure.

The expected risks are those commonly described during tracheal intubation in the newborn: bradycardia, desaturation, trauma to the upper airways. Premedication should avoid pain and discomfort, but expose children to the theoretical risk of chest stiffness and low blood pressure. The interpretation of arterial hypotension in preterm infants is extremely difficult [57]. Indeed, it has been shown that the correlation between blood pressure and cardiac output is poor in these children [58]. Upper vena cava flow was more predictive of neurodevelopmental outcome at 3 years than arterial hypotension in premature infants [59]. However, routine measurement is difficult, especially during intubation.

Concerning neurodevelopmental outcome, no evidence in human clinical research (exclusively retrospective data) allows to fear a possible toxicity of non-surgical anesthetic treatment in neonates hospitalized in NICU[48,60,61]. However, short and long term neurological monitoring will be performed.

Description and justification of the route of administration, dosage, administration schedule and duration of treatment

The drugs studied are strictly reserved for the intravenous route. These treatments will be evaluated for a single episode of intubation corresponding to a single administration of the treatments.

Determination of doses

All children will receive atropine at a dose of 0.02 mg / kg IVD, ie 0.08 ml / kg of the 1 ml solution = 0.25 mg. This dose is routinely used in pre-anesthesia to prevent vagal bradycardias associated with the use of neuromuscular blockers[62]. Atropine will be routinely administered to prevent vagal stimulation associated with laryngoscopy [63].

Regarding propofol, the dose of 2.5 mg / kg was used for intubation of the preterm infant with no significant side effects, especially hemodynamic[51]. This study allowed a second injection of 2.5 mg / kg in case of failure of the first dose, which was necessary in 24% of cases [64]. In addition, a pharmacological study in the term and premature newborn showed that a single injection of 3 mg / kg resulted in rapid elimination of the product [65]. This same study established a slower elimination of the product in premature infants and children less than 10 days old. However, the occurrence of spontaneously resolving hypotension has been reported at a dose of 1 mg / kg in children younger than 8 hours [54]. Therefore, for the current study, a dose of 1 mg / kg is proposed, ie 0.1 ml / kg of propofol 1% in infants under 1000 g and 2.5 mg / kg, ie 0.25 ml / kg of propofol 1% in children over 1000 g, slow IV over 1 minute. If a satisfactory sedation (see criteria in chapter "Methods") is not obtained an additional dose of 1 mg / kg (ie 3.5 mg / kg maximum cumulative dose), or 0.1 ml / kg, may be administered. Propofol 1% will be increased to a volume of 1 ml in children under 1000 g to allow injection over 60 seconds. It will be used pure for children over 1000 g.

If a patient is randomized to the atropine-sufentanil-atracurium group, he or she will receive atracurium after atropine to prevent the risk of sufentanil-related chest rigidity. A dose of 0.3 mg / kg of atracurium will be used. The dose of 0.5 mg / kg has been shown to be effective in neonates [66,67], as is the dose of 0.3 mg / kg in only 10 patients [67]. Efficient dose-finding studies have established an effective dose range of 0.3 to 0.7 mg / kg in neonates [68,69]. Finally, the occurrence of rare accidents in the United Kingdom has recommended a dose of 0.25 mg / kg in newborns [70]. We propose for this study a dose of 0.3 mg / kg corresponding to the local experience at Créteil's NICU[50]. The atracurium besilate will be diluted according to the following modality: 1ml = 10 mg in 9 ml of D5% resulting in a solution diluted to 1 ml = 1mg. 0.3 ml / kg (ie 0.3 mg / kg) of the IV

diluted solution over 30 seconds will therefore be administered. In case of insufficient sedation, an additional dose of 0.1 ml / kg (ie 0.1 mg / kg) may be administered after the injection of sufentanil. Finally sufentanil will be injected. The loading dose of 0.2 µg / kg has been reported twice in the literature in neonates [71,72], with both efficacy and good tolerance. In addition, it is regularly used in Créteil's NICU[50]. Very high doses (5 to 15 µg / kg) were administered in neonatal cardiac surgery with good tolerability and improvement in operative follow-up compared to the morphine-halothane group [73]. However, in view of the pharmacokinetic peculiarities of extremely low birth weight neonates, a dose of 0.1 µg / kg should be used in infants <1000 g and 0.2 µg / kg in infants > 1000 g. Sufentanil will first be diluted according to the following scheme: dilute 1 ml = 5 µg in 4 ml of D5% resulting in a solution diluted to 1 ml = 1 µg. 0.1 or 0.2 ml / kg (0.1 or 0.2 µg / kg) of the diluted IV solution will be administered depending on the weight groups over 60 seconds to reduce the risk of thoracic rigidity. In the group of infants<1000 g, the volume of the syringe will be increased to 1 ml to allow injection over 60 seconds. In infants> 1000g, the drug will be used diluted according to the above-mentioned modalities.

With regard to the placebo for the studied drugs, the volumes of normal saline used in the propofol arm (0.5 ml maximum cumulative volume in children <1000 g and 0.6 ml / kg in children> 1000 g) are considered negligible and without any effect on the blood volume or ionogram because they are lower than the flushing volumes currently used in daily practice. The volume of intralipids 20% used in the sufentanil + atracurium arm represents a maximum of 0.2 ml / kg (<1000g) or 0.35 ml / kg (> 1000 g) cumulative volume. These intakes correspond respectively to 0.04 g / kg (<1000 g) and 0.07 g / kg of purified soybean oil. These minimal intakes do not affect global nutrient intakes of the order of 2 to 3 g / kg / 24h of lipids.

Declaration of compliance with the protocol, good clinical practices and the legal and regulatory provisions in force

The participating investigators undertake to respect the study protocol and to comply with the good practices in force. The legal and regulatory provisions in force will also be respected.
The choice of the atropine-opioid-neuromuscular blocker combination for the control group corresponds to the recommendations of the literature [14,18,23]. The choice of atropine-propofol is based on the pharmacological properties of propofol and the encouraging literature [51,55,56].

Description of the population to be studied

The study will include all premature or term neonates requiring tracheal intubation outside the context of the vital emergency and not presenting a contraindication to the use of the different experimental treatments (see criteria for non-inclusion). These children will be divided into two groups according to their weight at the time of intubation.

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Purpose and outcomes

Purpose

The aim is to compare two premedications: atropine-propofol and atropine-atracurium-sufentanil regarding desaturationsduring neonatal tracheal intubation on one hand, and regarding efficacy and tolerance.on the other hand

Hypothesis

"atropine + propofol" compared to "atropine+atracurium+sufentanil" will significantly reduce the frequency of severe hypoxemia.

Primary outcome

Pulse oxymetry value < 80% for more than 60 seconds.

Since desaturation is defined as O2 saturation of less than 80% for at least 60 seconds, the main objective is to show that premedication with propofol decreases the frequency (percentage) of children with episodes of desaturation during tracheal intubation, the control group receiving atracurium-sufentanil. Both groups will receive atropine beforehand.

Secondary outcomes

Number of attempts, duration of the procedure, quality of sedation, time to spontaneous respiratory and limb's movements' recovery, changes in physiologic parameters, short- and long-term neurodevelopmental outcomes.

The secondary objectives are to confirm the following assumptions:

Compared to the atracurium-sufentanil association as premedication before intubation,

- propofol will decrease the number of intubation attempts
- propofol will reduce the duration of intubation
- propofol will maintain the physiological parameters close to the basal state
- Propofol will not cause short- and long-term neurological adverse events (2 years)

Methods

Trial design

Study Type: Interventional, multicenter

Allocation: Randomized

Intervention Model: Parallel Assignment

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Primary Purpose: Treatment

Study proposal and consent from parents

The protocol will be exposed to the parents of all infants admitted to the to the neonatal intensive care unit.Parents will be informed about the objectives, methods, expected benefits and potential risks of the study and any inconvenience this may cause to their child. In cases where only one parent is present (absent father or mother hospitalized in another maternity and not immediately transportable), the written informed consent can be obtained from the present parent and the oral consent by telephone from the absent parent, who will sign the consent form as soon as he / she can move. This procedure should remain exceptional if no other solution to meet the parents directly is possible. Parents can also be approached if an upcoming intubation is planned and they are both present. Parents should be informed that they are free to revoke their consent at any time. The investigator will attest by affixing his / her signature at the bottom of the "Consent Form" that he / she has delivered all of the information contained in the information form.
The parent (s) will certify by their signature on the same form that they have received this information and that they voluntarily participate in the project without any pressure being exerted on them.
Once signed, the original will be archived by the investigator, a copy will be transmitted by the CRA monitor to Activ in sealed envelope in order to respect the anonymity of the subject and a copy will be given to the parents. In case of intubation in an eligible infant with signed parental consent, the child will be included in the study and the parents will be notified according to the usual local practices (telephone call or interview, immediately or after a delay).

Data collection

A team member who will not be directly involved in the intubation procedure will be designated as an "observer". He/she will be responsible for the collection of data.
The child's birth date, age and corrected age, birth weight and current weight, sex, 5 minutes Apgar score, reason for intubation, personal history of intubation and last cranial ultrasound will be recorded before the start of the procedure. If the child had nocranial ultrasound performed within the previous 7 days, one should be performed before inclusion.

The collection of the physiological parameters will begin 1 minute before the first injection and will be continued one hour after. Heart rate, pulse oximetry and blood pressure will be obtained one minute prior to injection of the first drug (atropine) and will be used as the baseline. Throughout the procedure, heart rate, transcutaneous CO2 partial pressure (TcPCO2) and oxygen saturation will be monitored continuously and blood pressure will be measured every three minutes by the monitoring system used in each service. O2 saturation will be measured by oximeters using Masimo technology [74] in all participating centers. Heart rate, blood pressure, O2 saturation, TcPCO2, cerebral activity via cerebral oximetry and ventilatory constants will be recorded 1 minute before the first injection, then 3, 6, 9, 12, 15, 30, 45 and 60 minutes after the start of the first injection.

The observer will collect vital parameters before the procedure and then, during the procedure, the lowest heart rate, lowest saturation and the lowest and highest arterial pressures. He/she will measure the duration of intubation, the recovery time of spontaneous ventilation and the recovery time of spontaneous movements after the first drug injection. By controlling on the central monitor recordings, he/she will confirm the occurrence of the primary outcome (desaturation of less than 80% for at least 60 seconds). This recording of physiological data will be stored and printed or saved in a digital format as source data. If no record can be made, the handwritten record sheet completed by the observer will serve as source data.

The time will be measured from the insertion at the last ablation of the laryngoscope form the mouth after the success of the intubation. Intubation will be considered successful by clinical confirmation of bilateral lung sounds on auscultation, increased heart rate and saturation, and by the presence of an inspiratory and expiratory curve obtained through the respirator's spirometry sensor. In both groups, the duration of action of the drugs administered will be noted.

A standardized collection sheet will indicate the level of training of the operator, the number of attempts for each operator, the total number of attempts required and the existence of any complications such as thoracic stiffness, lacerations of the mouth or lips.

For neurological surveillance, aHUS will be performed within 7 days of intubation and will be compared to the pre-intubation examination if it exists. The follow-up of the children will be performed in each unit during outpatient visits at the corrected ages of one and two years. A questionnaire corresponding to the French version of the questionnaire Age and Stages Questionnaire (ASQ) [75]will then be completed. In the absence of outpatient visits, parents will be called by telephone at the same dates and asked to complete the same questionnaire.

Intervention

After randomization and when the drugs are ready for use, the patient will be equipped with a pulse oxymetry sensor on his right hand. He/she will be positioned in the incubator and pre-oxygenated thanks to an artificial ventilation system connected to a face mask and delivering a positive expiratory pressure (PEP): respirator or bag equipped with a PEEP valve, with an FiO_2 allowing to

obtain an SpO_2 ≥ 95%. The intubation will be performed by ajunior or senior doctor with a laryngoscope and an appropriately sized endotracheal tube (ETT)through the orotracheal or nasotracheal route according to usual local practices. The common practice in the departments participating in the study is to use the nasotracheal route as first-line and to favor junior doctors as the first operator if the condition of the child allows it and under the supervision of a Senior doctor. In case of failure, the second operator is usually a senior. There will be no rule imposed on the sequence of the operators because this trial aims to compare the premedications under the usual conditions of practice of the neonatal intubations. However, the level of experience of the operator (s) will be collected in order to allow a possible adjustment to this criterion if the distribution between the groups is different.

weight ≤1000 g		
Syringe	**SufTrac group**	**Prop Group**
N°1	Atropine (1ml= 250 µg) 20 µg/kg 0.08 ml/kg IV bolus	Atropine (1ml= 250 µg): 20 µg/kg 0,08 ml/kg IV bolus
N°2 *Prepare syringe n°5 simultaneously*	Atracurium 1 ml= 10 mg + 9 ml 5%D: 0.3 mg/kg -> 1 ml= 1 mg : 0.3 ml/kg of the dilution IV 30 sec	Normal saline 1 ml + 9 ml 5%D 0.3 ml/kg of the dilution IV 30 sec
N°3	Sufentanil 1 ml =5µg + 4 ml 5%D: 0.1 µg/kg -> 1ml =1µg : 0,1 ml/kg of the dilution The volume of the syringe will be increased to 1 ml with 5%D to allow injection over 60 seconds	Normal saline 1 ml + 4 ml 5%D 0.1 ml/kg de la dilution The volume of the syringe will be increased to 1 ml with 5%D to allow injection over 60 seconds
N°4 *Prepare syringe n°6 simultaneously*	Intralipids 20%: 0.1 ml/kg Increase the volume of the syringe with 5%D for injection over 60 seconds, without exceeding 5 times the initial volume of the syringe	Propofol 1%: 1 mg/kg 0.1 ml/kg Increase the volume of the syringe with 5%D for injection over 60 seconds, without exceeding 5 times the initial volume of the syringe
N° 5	<u>If re-injection required :</u> Same dilution as syringe N°2 : 0.1 ml/kg	<u>If re-injection required :</u> Same dilution as syringe N°2 : 0.1 ml/kg

N° 6	<u>If re-injection required :</u> Same dilution as syringe N°4 : 0.1 ml/kg	<u>If re-injection required :</u> Same dilution as syringe N°4 : 0.1 ml/kg

The children will be randomized and 6 syringes will be prepared for each child: 4 syringes corresponding to the initial injections, 2 syringes for re-injections.

The contents of the syringes are illustrated in the following tables according to weight at randomization:

weight >1000 g		
Syringe	**SufTrac group**	**Prop Group**
N°1	Atropine (1ml= 250 µg) 20 µg/kg 0.08 ml/kg IV bolus	Atropine (1ml= 250 µg): 20 µg/kg 0,08 ml/kg IV bolus
N°2 *Prepare syringe n°5 simultaneously*	Atracurium 1 ml= 10 mg + 9 ml 5%D: 0.3 mg/kg -> 1 ml= 1 mg : 0.3 ml/kg of the dilution IV 30 sec	Normal saline 1 ml + 9 ml 5%D 0.3 ml/kg of the dilution IV 30 sec
N°3	Sufentanil 1 ml =5µg + 4 ml 5%D 0.2 µg/kg -> 1ml =1µg : 0.2 ml/kg of the dilution The volume of the syringe will be increased to 1 ml with 5%D to allow injection over 60 seconds	Normal saline 1 ml + 4 ml 5%D 0.2 ml/kg of the dilution The volume of the syringe will be increased to 1 ml with 5%D to allow injection over 60 seconds
N°4 *Prepare syringe n°6 simultaneously*	Intralipids 20%: 0.25 ml/kg Increase the volume of the syringe with 5%D for injection over 60 seconds, without exceeding 5 times the initial volume of the syringe	Propofol 1%: 2.5 mg/kg 0.25 ml/kg Increase the volume of the syringe with 5%D for injection over 60 seconds, without exceeding 5 times the initial volume of the syringe
N° 5	<u>If re-injection required :</u> Same dilution as syringe N°2 : 0.1 ml/kg	<u>If re-injection required :</u> Same dilution as syringe N°2 : 0.1 ml/kg
N° 6	<u>If re-injection required :</u> Same dilution as syringe N°4 : 0.1 ml/kg	<u>If re-injection required :</u> Same dilution as syringe N°4 : 0.1 ml/kg

The first 4 syringes will be injected to all children. If acceptable sedation is not achieved, syringes 5 and 6 will be injected.

Sedation will be satisfactory if the following 3 criteria are satisfied:

- Absence of facial expression,
- Absence of spontaneous movement,
- Absence of reaction to stimulation

In each group, if the oxygen saturation falls below 60%, the procedure will be stopped and ventilation will be resumed with the mask, attempting to increase the saturation to more than 90% within a maximum of three minutes. Beyond these three minutes, or earlier according to the

operator's judgment, a new intubation will be attempted. A "senior" will attend each intubation.

Outcomes

Primary Outcome Measure

- Desaturation: Pulse oxymetry value measured by Masimo technology below 80% for 60 seconds or more. Intubation procedure is defined by the time between first laryngoscope insertion and last laryngoscope removal after successful intubation. Successful intubation is defined by clear bilateral breath sounds, increasing heart rate and saturation (if previously low) and appropriate flow curves on the ventilator.

Secondary outcomes

- Number of intubation attempts: each insertion of the laryngoscope in the mouth is considered an attempt.
- Duration of intubation procedure: Duration of intubation is defined by the time between first laryngoscope insertion and last laryngoscope removal after successful intubation. Successful intubation is defined by clear bilateral breath sounds, increasing heart rate and saturation (if previously low) and appropriate flow curves on the ventilator.
- Heart rate: Heart rate recordings 1 minute before the first injection and at 3, 6, 9, 12, 15, 30, 45 and 60 minutes after the first injection
- Pulse oxymetry: Pulse oxymetry recordings 1 minute before the first injection and at 3, 6, 9, 12, 15, 30, 45 and 60 minutes after the first injection
- Mean blood pressure: Blood pressure recordings 1 minute before the first injection and at 3, 6, 9, 12, 15, 30, 45 and 60 minutes after the first injection
- Transcutaneous PCO2 (TcPCO2) measurement: TcPCO2 recordings 1 minute before the first injection and at 3, 6, 9, 12, 15, 30, 45 and 60 minutes after the first injection
- Time to spontaneous respiratory movements' recovery: Time between the first syringe injection and the first onset of the trigger logo of the ventilator used for conventional ventilation if a synchronized mode is used or first inspiratory effort through direct observation if high frequency oscillation or ventilation is used.
- Time to spontaneous limbs movements' recovery: Time between the first syringe injection and the first spontaneous limb movements' through direct observation of the neonate.
- Quality of sedation: Assessed immediately after completion of the procedure by the operator who succeeded the intubation according to the following scale adapted from Hans [76] and Cooper [77]:

Excellent: Relaxed jaw and open vocal cords and no movement when inserting ETT
Good: Relaxed jaw and open vocal cords and mild movements when inserting ETT
Acceptable: Mild jaw contraction and/or moving vocal cords and/or cough when inserting ETT

Poor: Jaw contraction or closed vocal cords or intense cough or rigidity when inserting ETT.

- Short term neurological outcome: Head ultrasound
- Long term neurodevelopmental outcome: Age and stages questionnaire (ASQ)

Measures to reduce bias

Randomization

Randomization will be centralized on line using a password. The randomization software will indicate the kit number to be used according to a pre-established randomization table stratified by center and by weight category. This assignment code will allow anonymization of the data. The programming of this randomization will be checked and validated by a second operator before putting it online.

To prevent a center from making almost all inclusions, which would impair the representativeness of the results, the number of patients per center will be limited to 100.

The number of inclusions may thus vary from one center to another, the important thing being that the two treatment groups remain balanced.

Masking

The placebo for propofol will be manufactured by Baccinex (Courroux, Switzerland) and will be sent to Theradis Pharma (Cagne-sur-mer, France). Kits containing 1 ampoule of atropine, 2 ampoules filled with a transparentfluid and 1 bottle of 50 ml filled with a white emulsion will be packaged and manufactured by the company Theradis Pharma (Cagne-sur-mer, France) according to the regulatory rules. The ampoules and vials will have a strictly identical exterior appearance between the verum and the placebo.

Dosage and ways of administration of treatments. Unit shape, packaging and labeling

The atropine used will be atropine sulfate RENAUDIN 0.25mg / ml for injection. Each 1 ml ampoule contains 0.25 mg of atropine.

Propofol Frésenius 1% is an injectable (oil-in-water, white and isotonic) emulsion in 50 ml vials. Each 50 ml vial contains 500 mg propofol, i.e. 1 ml contains 10 mg propofol. Excipients: soybean oil, egg lecithin, glycerol, oleic acid, sodium hydroxide, water ppi.

The atracurium used will be the Tracrium® GLAXOSMITHKLINE solution for injection 10mg / ml containing atracurium besilate in vials of 5ml = 50mg. Excipients: 32% benzenesulfonic acid solution qs pH 3 to 3.8, water.

Sufentanil JANSSEN (Sufenta\) 5µg / ml injectable solution is to be used. Each 10 ml vial contains 50 micrograms of sufentanil.Excipients: sodium chloride, sodium hydroxide qs pH4,5-7,0, hydrochloric acid qs pH4,5-7,0, water.
Placebo for propofol will be a 20% Intralipid lipid emulsion packaged in 250 ml glass bottles (Frésenius Kasbi) used for parenteral nutrition in newborns. This product will be deconditioned in sterile conditions by Baccinex and reconditioned in sterile conditions in 50 ml vials. Baccinex will perform autoclaving and stability feasibility tests prior to the start of the study.
The normal saline solution Lavoisier solution for injection will be packed in vials of 10 and 5 ml constituting respectively the placebo for sufentanil and atracurium. The "heads" of sufentanil and atracurium vials have specific colour linesthat do not appear on the "heads" of saline vials, Theradis Pharma will thus mask the heads of the 10 and 5 ml vials.

Duration of participation and follow-up

For the primary outcome, a patient will participate fromhis/her randomization to one hour after the first drug injection. For long-term follow-up, data collection is planned up to two-years corrected age.

Definitive or Temporary Termination Rules

For an included patient

Since the trial involves a single prior administration of the medicinal product, participation may only be halted if there is a serious adverse reaction during the course of treatment or in case of sedation deemed insufficient by the operator: the operator will then administer the treatments deemed appropriate to the child's condition. However, data for this child will be analyzed (intention-to-treat analysis).

For the research

The research will be interrupted on the advice of the safety committee, which will examine serious adverse events that may or may not be attributable to the experimental treatments and suspend the study according to predefined criteria (see appropriate paragraph).

Treatment kits monitoring

Theradis Pharmawill deliver treatment kits to local pharmacies of the participating centers.
The distributed and administered treatments will be recorded on a list established by the center and containing the batch number of each kit as well as its expiry date. CTs and pharmacists will be responsible for updating this list and, in each center, the adequacy of treatments to inclusions.

Blinding maintenance and unblinding procedure

Unblinding will be performed at the request of the investigators or at the request of the supervisory committee.

An investigator will have the possibility to unblind the allocated treatment for a patient only if he/she considers that the knowledge of the treatments administered is indispensable to the care of the patient. In this case, he/she will obtain from the local pharmacy the sealed envelope corresponding to the patient. He/she will have to warn within 48 hours the investigating coordinator of the unblinding procedure.

The Safety Committee will have the possibility to waive blinding for one or several patients if a pre-defined number of serious adverse events occur, possibly or certainly attributable to the administration of drugs (see appropriate paragraph).

In all other cases, blinding will be maintained.

Source data

The source data for each patient will be recorded on an anonymized clinical research form (CRF), in each center, by the designated investigators, and collected by and centralized at ACTIV. The CRF will be verified and validated by the designated investigators at each center and the CRA. These CRFs will be kept under lock at the CHIC and duplicates will be kept in each participating center. In case of missing data or for the purpose of verification, access to the medical chart of each included patient will be granted to the CRA while respecting medical confidentiality.

Participants

Inclusion Criteria

Any newborn (corrected term <45 weeks of gestation) hospitalized in the neonatal intensive care unit and requiring non-urgent or semi-urgent intubation, equipped with a reliable and usable intra venous access, with parental consent, whowas never included in the study previously.

Non-Inclusion Criteria

- Lack of parental consent (failure to provide correct information to parents)
- Parental refusal
- Administration of sedative or anesthetic treatment in the previous 24 hours
- Hemodynamic failure defined by a mean arterial pressure <corrected GA and / or capillaryrefill time> 3 seconds
- Evidence of ENT malformation orobvious condition suggesting especially difficult intubation
- Life-threatening situation requiring intubation without premedication
- Participation in another exclusive clinical trial
- Impossibility of placing intra venous access
- Known intolerance to sufentanil or to opioids

- Association with morphine antagonists: nalbuphine, buprenorphine, pentazocine
- Risk of glaucoma
- Paralytic Ileus
- Urethro-prostatic disorders with risk of urinary retention
- Known hypersensitivity to propofol, soybean, peanuts, or any of the excipients of the emulsion
- Allergy to soya or peanuts
- Hypersensitivity to atracurium, cisatracurium or benzene sulfonic acid
- Acute shock
- Severe dyslipidemia
- Severe hepatic failure
- Severe coagulation disorders,
- Known or suspected hypersensitivity to egg phospholipids, soybean or peanut proteins or to any of the active substances or to any of the excipients contained in the intralipids.

Procedures for prematuretermination of treatment administration and for patient's exclusion

Criteria and procedures for discontinuing treatment and excluding a person from research

Premature discontinuation of treatment can only occur in the case of a serious adverse effect during treatment (exceptional situation). The criteria for the immediate cessation of intravenous injection during treatment are:

- Sudden appearance of a lesion at the injection site
- Central circulatory disorders with tachycardia> 200 / min or bradycardia <60 / min. In the event of a state of shock, volume expansion and inotropes must be readily available for each intubation.

A patient will be excluded from the search if the parents withdraw consent.

Method and timing of data collection

Premature cessation of treatment or a patient's exclusion should be transmitted within two working days to the coordinating investigator. A summary of these data will be made every 3 months.

Modality for the replacement of excluded patients

No alternative arrangements are planned, these circumstances being considered as exceptional.

Follow-up

In the short term, monitoring will be continuous (see methodology).

In the medium term, a head ultrasound should be performed within 7 days after the patient's inclusion. All serious adverse events occurring within one week after inclusion of a patient should also be collected and reported (see appropriate paragraph).
In the long term, neurodevelopmental follow-up will be carried out during outpatient visits or by phone. Clinical evaluation will be performed during outpatient visits within each participating center.
The telephone assessment will be carried out at the corrected ages of one and two years according to the French version of the Age and Stage Questionnaire (ASQ)[75].

Treatments given to participants

Description of the treatments needed to carry out the research

The treatments used (atropine, propofol and atracurium-sufentanil combination) have been previously described in this Protocol.

Medicinal products and treatments authorized and prohibited under the Protocol

Administration of a sedative or anesthetic treatment within 24 hours prior to intubation constitutes a non-inclusion criteria in the study.
The administration of a morphine agonist-antagonist treatment is contraindicated within 24 hours of inclusion.
Any treatment deemed necessary for the patient is permitted. In the absence of extreme agitation or obvious pain, no sedative or anesthetic treatment should be administered within 1 hour of the study treatment.

Method for treatment follow-up and compliance

The treatment kit assignment will be done after randomization under the prescription of the doctor carrying out the study in each unit.
The kit number assigned to each patient will be printed and included in the CRF.
The volumes of each injected solution will be recorded during the study by direct observation.
Given the uniqueness of the administration, no compliance problems are to be feared.
The remaining quantities of unused product will be disposed of and empty vials will be sent to the local pharmacies at each center for posting and tracking of batches.

Storage conditions of experimental drugs

Propofol can be stored at a temperature not exceeding 25 ° C. It can also be stored at + 4 ° C, at which temperature its stability is 36 months. It must be used within 6 hours of its preparation. The unused quantity should be discarded.
Atropine can be stored at room temperature or between + 4 ° C and + 8 ° C (lab advice Aguettant).

Sufentanil may be stored at room temperature at a temperature not exceeding 25 ° C. It should be used within 24 hours of its preparation. The unused quantity should be discarded.
Atracurium should be stored in the refrigerator (between + 2 ° C and + 8 ° C) and should not be frozen. The ampoules should be stored in the box in order to protect them from light. Once prepared, atracurium should be used immediately. The unused quantity should be discarded.
Lavoisier sodium chloride 0.9 per cent solution for injection, packaged in glass vials requires no special storage precautions.
Intralipids 20% Fresenius must be stored at a temperature below 25 ° C.
The study kits will therefore be stored between + 2 ° C and + 8 ° C in a locked refrigerator provided to the centers by the sponsor for study purposes. The key of this refrigerator will be kept and made available in each pharmacy for internal use according to the same modalities as the key allowing the access to narcotics.
Within Theradis Pharma, under the procedure "Management of narcotic drugs and psychotropic drugs":
The narcotics are stored in a locked area, access to which is protected by a grid. This room contains nothing but narcotics. It is also equipped with a refrigerator and a freezer for special storage conditions.
Only the Responsible Pharmacist and the Quality Assurance Manager of the Pharmaceutical Affairs know where the key is located.

Efficacy assessment

Description of Efficacy Assessment Parameters

The efficacy of premedication will be evaluated according to the previously stated criteria for sedation to be achieved within two minutes of administration:
- Absence of facial expression,
- Absence of spontaneous movement
- Absence of reaction to stimulation

The efficacy of propofol compared to the atracurium-sufentanil combination will be evaluated by a significant decrease in the frequency (percentage) of children with desaturation <80% for at least 60 seconds.

Method and timeline for measuring, collecting and analyzing efficacy endpoints

Episodes of desaturation <80% for at least 60 seconds will be identified by continuous monitoring analysis. The data collected for each patient, including the number of desaturations, will be collected every three months in each center by a CRA. The frequency of visits may be adapted to the inclusion rate of each center.

At the end of the study, the analysis will cover all studied infants.

Safety assessment

Safety assessment Parameters

An adverse event (AE) is defined as any adverse event in a patient in a clinical trial that is not necessarily linked to the treatment provided in the clinical trial. All adverse events encountered during the study will be recorded in the CRF in the dedicated section.This study falls within the scope of the law of 20 December 1988, as amended, protection of persons who lend themselves to biomedical research, the measures necessary to ensure that the provisions of Article L. 209-12 6th paragraph of the Public Health Code are respected, will be implemented. In particular, all serious adverse events likely to be related to the research will be reported. The investigators of each center will be responsible for establishing the accountability of the experimental treatment for the occurrence of the adverse event according to 3 modalities:

- not attributable;
- possibly attributable;
- certainly attributable.

A serious adverse event will be a serious adverse event that is either possibly or certainly attributable to one or more of the experimental drugs.

The investigator is responsible for informing the sponsor of any serious adverse event. Responsibility for reporting such events to the supervisory authorities rests with the proponent.

Serious adverse events (SAEs) are considered to occur when an AE:

- Causes death,
- Involves the vital prognosis,
- Causes a temporary or permanent disability or incapacity,
- Requires or extends the hospitalization of a patient.

Some of the serious adverse events are listed in the following list, which is however not exhaustive:

- Deaths
- Heart failure
- Pneumothorax
- Sepsis
- Necrotizing enterocolitis
- Grade III or IV intraventricular haemorrhage
- Neurological lesion (peri-ventricular leucomalacia, ischemia, haemorrhage)

- Severe metabolic acidosis (pH <7.00, excess of base <15 mmol / l)

Methods and schedule for AE declaration

AEs will be collected within one hour of the start of treatment.
Investigators will be required to report the occurrence of any SAE that appears within seven days of inclusion. The declaration of these SAEs must be made without delay to ACTIV as soon as the investigator of the center becomes aware of it. The SAEs will be analyzed in real time.

Procedures for registration and notification of adverse reactions

The AEs will be recorded in the CRF after the CRA has verified the data.
- Serious adverse events (adverse events possibly or certainly attributable to experimental treatments) will be counted as they are notified and may lead to discontinuation of the study. The pharmacovigilance unit of For Drug Consulting is responsible for analysis and declarations to the competent authorities. The safety committee will be composed of Dr Sophie Saizy-Callaert, pharmacist at CHIC, Prof. Gilles Dhonneur, Anaesthesiologist- Intensivist at the CHU Henri Mondor and a Neonatologist, Dr. Elisabeth Walter, neonatology department, Hôpital Saint Joseph, Paris. The rules for stopping the study will be as follows:
    - Occurrence of two deaths directly attributable to the administration of drugs (frequency 1%);
    - Occurrence of three cardiac arrests requiring external cardiac massage and / or adrenaline administration directly attributable to drug administration (frequency 1.5%)
    - Occurrence of twelve new episodes of intraventricular haemorrhage grade III or IV and / or leucomalacia within 7 days of administration in the population of children under 1000 g (frequency 15%).

These SAEs leading to study interruption will be communicated by the study coordinator via e-mail to the investigators of each center who will be responsible for their transmission to the rest of the team.
The protocol, patient information note and consent may be amended if new safety information is updated.

Follow-up of persons following the occurrence of adverse events

Follow-up will be the one planned for the study. In case of a SAE, follow-up adapted to the patient's state of health and corresponding to the usual practices of the service will be offered.

Statistics

Statistical methods and timing of intermediate analysis

Initial analysis plan (as of September 2011) not executed

Pretreatment characteristics between groups (sex, gestational age, chronological age and corrected age, birth weight and present weight, 5-minute Apgar score, oxygen saturation, blood pressure, cardiac and respiratory rate, history of intubation, intubation) will be compared using Mantel and Haenzel tests (sex, gestational age, 5-minute Apgar score) or 2-factors variance analysis (all other variables). The randomization is stratified on the weight of the child at the time of intubation and on center, the two groups will be not be compared for these characteristics because of the randomization process.

Analysis of primary and secondary outcomes (frequency of the children with desaturation, SpO2, blood pressure and heart rate, number of attempts and total duration of intubation) will also involve the Mantel and Haenszel test (frequency of the children with desaturation, indication for intubation and number of intubation attempts) and analysis of variance (for total duration of intubation).

A subgroup analysis according to weight categories will be performed if the interaction test (chi2 homogeneity) shows a difference in the effect of premedication on the primary outcome according to weight categories.

No interim analysis is planned, the continuation of the study being based on the previously defined stopping rules.

Final analysis plan *(as of November 2016, established before data was released)* executed

Pretreatment characteristics (sex, gestational age, chronological age and corrected age, birth weight and present weight, 5-minute Apgar score, oxygen saturation, blood pressure, cardiac and respiratory rate, history of intubation, intubation) will be described by groups and no statistical test will be performed to compare the two groups at baseline.

For the frequency of children with desaturation (primary outcome) and worsening of head ultrasound, the analysis will be conducted according to the intent to treat principle using a generalized mixed model with a log-binomial distribution adjusted on weight at inclusion (≤1000g, >1000g) accounting for randomization structure and treating center as a random effect (exchangeable within-center correlation structure). Generalized linear mixed models are an extension of linear mixed models to allow response variables from different distributions, such as binary responses, which is the case for our primary outcome. In that type of model, we have to

specify the distribution of the variable to explain (ie, the outcome). For the primary outcome, which is a binary outcome, we used a log-binomial distribution to obtain an adjusted relative risk.

The number of intubation attempts will be analyzed using a generalized mixed model with a log-Poisson distribution to account for the nature of variable (ie, counting with one or more several intubation attempts by patient).

Duration of intubation will also be evaluated using a generalized mixed linear model. The duration of intubation, the quality of sedation and the time to respiratory and limbs' movements' recovery will be compared between treatment groups using Kruskal-Wallis tests.

The analysis of variations in physiological parameters recorded at the predefined time points will be performed using a generalized linear model for repeated data including treatment group, time, time by treatment interaction, baseline parameter value, weight at inclusion (≤ 1000g, >1000g) and treating center as a random effect (exchangeable within-center correlation structure).

A subgroup analysis will be conducted according to weight at inclusion (≤1000g, >1000g).

No interim analysis is planned, the study being based on pre-defined stopping rules.

Sample size

If one wants to show that the frequency of children showing at least one desaturation decreases significantly from 50% to 30% assuming a 2-sided α error of .05 and a power of 0.8, 93 children per group are required, ie 186 children in total .

Given that 40% of children should weight less than 1000 g and 60% more than 2000 g, 37 and 56 children in each group should be included in each stratum: for 5 participating centers, this would result in 8 children per group for weights ≤ 1000 g and 12 children per group for weights> 1000 g.

Taking into account possible withdrawals of consent, recruitment could be carried out by 5 centers according to the following scheme:

Center	weight ≤ 1000 g		weight> 1000 g	
	A	B	A	B
1	8	8	12	12
2	8	8	12	12
3	8	8	12	12
4	8	8	12	12
5	8	8	12	12

which would eventually require 200 children.

Expected statistical significance

A difference observed between the two groups will be said to be significant if p <0.05.

Statistical Criteria for Stopping the Research

No interim analysis is planned. The rules for stopping the test are defined in another paragraph.

Method for taking account of missing, unnecessary or invalid data

Missing data will not be accounted for.

Management of changes to the initial strategy analysis plan

Not applicable to this study.

Choice of subjects to include in analyzes

The analysis will be on an intent-to-treat basis and will include all randomized children, even if incomplete treatment or ineffective sedation is used.

Regulatory and Ethical aspects

Right of access to data and source documents

Access to data will be authorized for the CRA, the coordinating investigator and the sponsor in compliance with the rules of medical confidentiality. Direct access to source data will be authorized by the investigator in the event of an audit by the proponent or representatives of regulatory authorities.
The source documents will be stored in each center inCRFs composed of single sheets. The copy will be collected by the CRAat each center and the original will be retrieved during the monitoring visits and stored in the Neonatal Resuscitation and Neonatal Department of CHIC, under lock.

Quality control and quality assurance

The completeness, consistency and quality of the data collected will be ensured by the investigators designated in each center and verified by the CRA. The principal investigator reserves the right to exclude from the study a center that does not conform to the protocol or does not ensure correct data collection

Ethical Considerations

This study will be carried out according to the national ethical rules for minors suitable for biomedical research. This protocol shall be submitted by the coordinating investigator to the opinion of the Comité de Protection des Personnes Ile de France III in accordance with the legislation in France at the start of the trial. Upon receipt of the favorable opinion issued by the Comité de Protection des Personnes and registration of the study at the General Direction of Health, the study may begin.

Declaration of Helsinki

This project was developed and will be carried out in accordance with the principles laid down by the 18th World Medical Assembly in Helsinki in 1964 and their amendments adopted in Tokyo, Venice, Hong Kong, South Africa and Edinburg - Ethical and legislative texts on Biomedical Research).

It also complies with the legislation in France (Huriet Law No. 88-1138 of 20 December 1988, as amended, and Public Health Act No. 2004-806 of 9 August 2004) and the "Notice to Promoters and Investigators clinical trials of medicines "published by the Ministry of Health and Family in 1987 (see Ethical and Legislative Texts on Biomedical Research).

National Agency for Numerical Data Safety (CNIL)

The study is subjectedto a declaration to the CNIL, and complies with the criteria for the methodology of reference.

Data processing and retention of research documents and data

Data processing: CRFs will be sent to ACTIV for validation, and dual input in real time. Requests for correction on the already monitored CRFs will be edited by ACTIV in the form of queries and handed over to CRA monitors in case of missing or incorrect data. Following the monitoring visits, the dated and signed investigator's responses will be entered on the basis, once refastened to ACTIV.

The data will then be treated anonymously by Dr. Dechartres and Mrs Martin-Marchand (INSERM U 1153), respectively methodologist and statistician appointed for this study.

The source documents will be kept in the participating centers and at the CHIC for a period of 15 years.

The documents to be kept by the investigator for a period of 15 years are as follows:

- the final protocol signed by the investigator
- any amendments to the protocol
- one copy of the FIU for each patient
- an information form
- a patient identification list
- Completed FIUs (yellow leaflets)
- his CV together with an original copy of his financial agreement

- signed (original) consents

Funding and Insurance

Funding for the study is based on funding through PHRC 2009, combined with an accepted supplement in September 2014. No other funding was requested for this study. The application for funding included in this study takes into account the cost of medical and paramedical time in all centers (two full-time equivalents for the entire study), the cost of the CRA and its regular movements. Regarding drugs, prices were evaluated with the CHIC pharmacy but will be fixed after the procedure respecting the code of the public contracts. Costs related to the double-blind procedure (pharmaceutical manufacturers) are based on a detailed quote from Crid Pharma, Theradis and Baccinex. Pharmacovigilance fees are based on quotes from the company ForDrug Consulting.
The CRA of each site will ensure data entry. CRC monitors from CHI Créteil will monitor the study. Insurance has been taken out in accordance with the provisions of article L.1121-10 of the Code of Public Health. Issue 102.760 by the sponsor to SHAM.

Publication rules

The results of this study will be published in an international peer-reviewed English-language journal.
Excluding the first and last author ranks reserved for the coordinating center, the rank will be proportional to the number of inclusions for each center. A representative of ACTIV will also be among the authors.

Feasibility of the study

Each participating center has a high annual recruitment. They all have solid experience in multicenter clinical trials. In the prospective study carried out in Creteil's NICU in 2007, 35 newborns (all gestational ages) were intubated over a period of 6 months (personal data), ie 70 intubations per year. It can therefore be estimated that in each center - the number of annual neonatal admissions is close to that of the CHIC - an average of the lowest of 60 intubations per year will be achieved (90 over 18 months). The target of 40 inclusions per center over 18 months therefore requires an inclusion rate of 44% in the eligible population. This rate appears to be reasonably achievable given the experience of each of the participating centers. In each center, a part-time research technician will be allocated to identify eligible patients and provide first information to parents of potentially eligible children. These research technicians will also be responsible for the quality and completeness of the data collection, the appropriate reporting of AEs and SAEs by investigators and the keeping of screening logs. The inclusion rate of each center will be evaluated by the weekly collection of all the intubations carried out ("screening log") which will be transmitted by fax to the coordinating center. In case of difficulties of inclusion, the

reasons for these difficulties will be discussed with each center and appropriate measures will be taken during on-site visits.

The proper implementation of the study will be ensured by prior visits to each center explaining the objectives of the protocol, its conduct, the modeling with training in data collection, the declaration of AEs and SAEs and to plan the CRA's visits.

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