Rapid Sequence Induction is Superior to Morphine for Intubation of Preterm Infants: A Randomized Controlled Trial

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Objectives To compare rapid sequence intubation (RSI) premedication with morphine for intubation of preterm infants.

Study design Preterm infants needing semi-urgent intubation were enrolled to either RSI (glycopyrrolate, thiopental, suxamethonium, and remifentanil, n = 17) or atropine and morphine (n = 17) in a randomized trial. The main outcome was "good intubation conditions" (score ≤10 assessed with intubation scoring), and secondary outcomes were procedural duration, physiological and biochemical variables, amplitude-integrated electroencephalogram, and pain scores.

Results Infants receiving RSI had superior intubation conditions (16/17 versus 1/17, $P < .001$), the median (IQR) intubation score was 5 (5-6) compared with 12 (10.0-13.5, $P < .001$), and a shorter procedure duration of 45 seconds (35-154) compared with 97 seconds (49-365, $P = .031$). The morphine group had prolonged heart rate decrease (area under the curve, $P < .009$) and mean arterial blood pressure increase (area under the curve, $P < .005$ and %change: mean ± SD 21% ± 23% versus −2% ± 22%, $P < .007$) during the intubation, and a subsequent lower mean arterial blood pressure 3 hours after the intubation compared with baseline ($P = .033$), concomitant with neurophysiologic depression ($P < .001$) for 6 hours after. Plasma cortisol and stress/pain scores were similar.

Conclusion RSI with the drugs used can be implemented as medication for semi-urgent intubation in preterm infants. Because of circulatory changes and neurophysiological depression found during and after the intubation in infants given morphine, premedication with morphine should be avoided. *(J Pediatr 2011;159:893-9)*.

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Endotracheal intubation without preceding analgesia and sedation is painful and associated with acute increases in blood pressure and intracranial pressure, bradycardia, and hypoxia[1,2] and may cause neurological complications.[3] Current recommendations indicate that elective and semi-urgent intubations in infants should be performed after premedication.[4,5] However, no evidence-based consensus is available, and treatment strategies vary.

Morphine is used as an analgetic before intubation despite the slow onset and long duration of action.[5] The benefits of muscle relaxants were reported in 1989[6] and later verified in a randomized controlled trial (RCT).[1] In placebo controlled trials, superior intubation conditions were found with the sedative thiopental[7] and a combination with morphine and suxamethonium,[8] but not with morphine alone.[9]

Optimal premedication should eliminate pain, discomfort and physiological instability, and provide conditions for rapid and safe intubation without adverse effects. This can be achieved with a combination of drugs administered as a "rapid sequence induction/intubation" (RSI), which includes a vagolytic agent to prevent bradycardia and airway secretions, sedative and analgesic drugs to assure depressed consciousness and pain control, and a muscle relaxant to suppress muscular activity.[5,10] With increasing use of nasal continuous positive airway pressure in preterm infants, instillation of surfactant should preferably be given with the INSURE (Intubate, Surfactant, Extubate) procedure,[11] for which a short-acting RSI would be optimal. A RSI regimen is also useful when prolonged mechanical ventilation is needed.

aEEG	Amplitude-integrated electroencephalogram
AUC	Area under the curve
EEG	Electroencephalogram
HR	Heart rate
MABP	Mean arterial blood pressure
NICU	Neonatal intensive care unit
RCT	Randomized controlled trial
$rScO_2$	Regional cerebral oxygenation
RSI	Rapid sequence induction
SpO_2	Peripheral oxygen saturation

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Trial registered with EudraCT (2004-001583-52) and www.clinicaltrials.gov (NCT00216944).

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Sick preterm infants need intensive care during a period of a rapidly developing and highly vulnerable central nervous system and an immature hemodynamic state. Most analgesic and sedative drugs cause arterial hypotension and have potentially compromising cerebral adverse effects.[12-15] These drug effects can be detected by using bedside monitoring technologies, such as near-infrared spectroscopy[16] and amplitude-integrated electroencephalogram (aEEG).[17,18]

Our aim was to develop a RSI premedication for preterm infants and compare this with traditional morphine use in a RCT with special focus on the intubation procedure, stress/pain and need for additional analgesics, and potential short-term adverse events. The RSI was designed when very few premedication RCTs had been published,[1,7-9] and the selected drugs were all short-acting and previously used in newborns. Glycopyrrolate is a synthetic anticholinergic agent.[19] Thiopental is a potent short-acting sedative, used for induction of anesthesia.[7] Suxamethonium is a depolarizing neuromuscular blockage agent, and remifentanil is a synthetic opioid, both with a rapid onset and short offset of action.[6,8,19]

Methods

The study was carried out from July 2005 to October 2009 at Lund University Hospital with a tertiary level neonatal intensive care unit (NICU). The Competence Centre for Clinical Research at Lund University Hospital was responsible for monitoring, and a safety committee surveyed adverse events. The Regional Ethics Committee in Southern Sweden and the Medical Products Agency in Sweden approved the research protocol. The trial was registered with EudraCT (2004-001583-52) and www.clinicaltrials.gov (NCT00216944). Written informed consent was obtained from both parents.

The randomization (**Figure 1**, A; available at www.jpeds.com) was performed with blocks of 4 (2:2 allocation ratio), with stratification for gestational age and postnatal age. Group allocation with drug dilution and administration regimen was provided in sealed envelopes. All investigators, medical and nursing staff, and the parents were masked as to the study group assignment.

Inclusion criteria were gestational age <37 weeks and no administration of analgesics or sedative drugs during the previous 24 hours. Exclusion criteria were asphyxia (10-minute Apgar score <4 or an umbilical cord pH <7.0), serum potassium level >6 mmol/L, major malformations, and postoperative care.

The infants were randomized to receive intravenously atropine and morphine or the combination of glycopyrrolate, thiopental, suxamethonium, and remifentanil. To counteract a blood pressure drop after drug administration, a saline infusion of 5 mL/kg was given to infants who had never received a transfusion. The dosage of the drugs was calculated in relation to body weight and listed in precalculated tables with weight increment steps of 50 g. Only two nurses who prepared and administered the drugs were aware of group allocation. To maintain blinding, similar amount of solutions (with saline as placebo) were administered with identical clear syringes numbered 1 to 5 in both groups (**Figure 1**, B). On clinical indication, decided by the intubating clinician, additional drugs could be given 5 minutes after the initiation of intubation.

Mean arterial blood pressure (MABP), heart rate (HR), and peripheral oxygen saturation (SpO_2) were recorded with Hewlett-Packard Monitor M1094A/ M1166A (HP, Kista, Sweden) and Nellcor N395 PulseOximeter (Nellcor Puritan Bennett, Pleasanton, California) and connected for concomitant data sampling to a Nervus Monitor 1.3 (Taugagreining HF, Reykjavik, Iceland) with a time-synchronized two-channel electroencephalogram (EEG)/aEEG. The electrodes were placed at F3, F4, Cz, P3, and P4 according to the International 10 to 20 system for continuous recording. Regional cerebral oxygenation/perfusion ($rScO_2$) was monitored with near-infrared spectroscopy (INVOS 5100C, Somanetics Corp, Troy, Michigan) during the intubation and for the next 20 minutes.

All intubations were performed nasally by experienced neonatologists. The total intubation time was measured from the insertion of the endotracheal tube in the nostril until the neonatologist considered it to be in the correct position. Number of attempts and time of last attempt were registered. Possible suction and bag-ventilation during the procedure were included in the total intubation time. The intubation conditions were scored by the neonatologist who performed it (**Figure 1**, C).[20]

Blood samples were repeatedly obtained (before, 20 minutes, 6 hours, and 24 hours after termination of intubation) for blood gas and plasma cortisol levels. Pain/stress were scored with Astrid Lindgren and Lund Children's Hospital Pain Scale for preterm infants (validated, unpublished, score range 0-10) every 30 minutes and Echelle Douleur Inconfort Nouveau-Ne scale[21] every 4 hours. All procedures were scored with Premature Infant Pain Profile.[22] Non-pharmacological and pharmacological pain treatment (morphine bolus, 0.15 mg/kg) was offered according to an algorithm on the basis of pain scoring. Cerebral ultrasound scanning was performed during the post-intubation 24 hours.

Outcome Measures

The primary outcome measure was "good intubation conditions," defined as a total intubation score ≤10, with all subitems scored ≤2 (**Figure 1**, C).[20] Duration of the procedure, biochemical (plasma cortisol), physiological (MABP, SpO_2, HR, and $rScO_2$), behavioral (pain/stress assessment), and neurophysiological (aEEG) changes during the procedure and the subsequent 24 hours were secondary outcomes.

Analyses

We estimated achieving a 30% improvement in number of infants with "good intubation condition" with RSI. To show this difference with a significance of 5% and power of 80%, 38 infants were needed. To compensate for a 5% drop-out, 40 infants needed to be recruited.

Physiological data were recorded at a sampling rate of 1 Hz, and artifacts were manually excluded before data