LUND UNIVERSITY

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

Norman, Elisabeth; Wikström, Sverre; Hellström-Westas, Lena; Turpeinen, Ursula; Hämäläinen, Esa; Fellman, Vineta

Published in:
Journal of Pediatrics

DOI:
10.1016/j.jpeds.2011.06.003

2011

Link to publication

Citation for published version (APA):
Norman, E., Wikström, S., Hellström-Westas, L., Turpeinen, U., Hämäläinen, E., & Fellman, V. (2011). Rapid Sequence Induction is Superior to Morphine for Intubation of Preterm Infants: A Randomized Controlled Trial. *Journal of Pediatrics*, *159*, 893-U45. https://doi.org/10.1016/j.jpeds.2011.06.003

Total number of authors:
6

General rights
Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.
• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: https://creativecommons.org/licenses/

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

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

E Norman, MD [1], S Wikström, MD [2,3], L Hellström-Westas, MD, PhD [2], U Turpeinen, PhD [4], E Hämäläinen, MD, PhD [4], V Fellman, MD, PhD [1,5]

[1.] Department of Pediatrics, Lund University and Lund University Hospital, Sweden

[2.] Department of Women's and Children's Health, Uppsala University, Sweden

[3] Center for Clinical Research, County Council of Värmland, Sweden

[4.] Department of Clinical Chemistry, Helsinki University Central Hospital, Finland.

[5.] Department of Pediatrics, University of Helsinki, Helsinki, Finland

Corresponding author*:*

Elisabeth Norman, MD

Neonatal Intensive Care Unit

Lund University Hospital, SE-221 85 Lund, Sweden

Tel +46-46-178068 Fax +46-46-178430

Mobile +46-705594340

e-mail: elisabeth.norman@med.lu.se

Keywords: premedication, remifentanil, thiopental, amplitude-integrated electroencephalography, near-infrared spectroscopy

Study registration:

EudraCT no 2004-001583-52 and www.clinicaltrials.gov NCT00216944.

Financial disclosure: The present study was supported by grants from Region Skåne (regional medical research grants), Lund University funds, Royal Physiographic Society in Lund and the

Jerring, Crafoord, Ekdahl and Elsa Lundberg and Greta Fleron foundations. SW was supported by grants from the County Council of Värmland and LWH by the Axelsson-Johnsson foundation. We declare no industry-relation and no conflicts of interest for authors or for co-workers referenced in the Acknowledgments section.

Abbreviations:

RCT – randomized controlled trial

GA – gestational age

GW – gestational weeks

PNA – postnatal age

NICU – neonatal intensive care unit

ETT – endotracheal tube

TIT – total intubation time

HR – heart rate

MABP – mean arterial blood pressure

SpO_2 – peripheral oxygen saturation

$rScO_2$ – regional cerebral oxygenation

nCPAP – nasal continuous positive airway pressure

EEG – electroencephalogram

aEEG – amplitude-integrated electroencephalogram

NIRS – near-infrared spectroscopy

Abstract

Objectives To compare rapid sequence intubation (RSI) premedication with morphine.

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. Main outcome was "good intubation conditions" (score ≤10 assessed with intubation scoring), and secondary outcome were procedural duration, physiological and biochemical parameters, amplitude-integrated EEG and pain scores.

Results RSI infants had superior intubation conditions,(16/17 vs 1/17, *P*<.001) median (IQR) intubation score was 5 (5-6) vs 12 (10-13.5, *P*<.001) and a shorter procedure duration, 45 (35-154) s vs 97 (49-365, *P*=.031). The morphine group had prolonged heart rate decrease (AUC, *P*<.009) and mean arterial blood pressure (MABP) increase (AUC *P*<.005 and %change: mean±SD 21±23 % vs -2±22%, *P*<.007) during the intubation, and a subsequent lower MABP at 3 h after the intubation compared to baseline (*P*=.033), concomitant with neurophysiologic depression (*P*<.001) for 6 h afterwards. Plasma cortisol and stress/pain scores were similar.

Conclusion RSI with the drugs used can be implemented as premedication 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.

Introduction

Endotracheal intubation without preceding analgosedation, 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 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 secretion, 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 (nCPAP) in preterm infants, instillation of surfactant should preferably be given by 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.

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 side-effects.[12-15] These drug effects can be detected using bedside monitoring technologies, such as near-infrared spectroscopy (NIRS)[16] and amplitude-integrated electroencephalogram (aEEG).[17, 18]

Our aim was to develop a RSI premedication for preterm infants, and compare this to 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 a synthetic opioid, both with a rapid onset and short offset of action.[6, 8, 19]

Patients and 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, 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 as EUDRACT no 2004-001583-52 and at www.clinicaltrials.gov . Written informed consent was obtained from both parents.

Design

The randomization (Figure 1A) was performed using blocks of 4 (2:2 allocation ratio), with stratification for gestational age (GA) and postnatal age (PNA). 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.

Patients

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

Study protocol

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 following 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 (using saline as placebo) were administered with identical clear syringes numbered 1-5 in both groups (Figure 1B). On clinical indication, decided by the intubating clinician, additional drugs could be given 5 min after the initiation of intubation.

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

All intubations were performed nasally by experienced neonatologists. The total intubation time (TIT) was measured from the insertion of the endotracheal tube into the nostril until the intubator considered it 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 TIT. The intubation conditions were scored by the intubator (Figure 1C).[20]

Blood samples were repeatedly obtained (before, 20 min, 6 h and 24 h after termination of intubation) for blood gases and plasma cortisol. Pain/stress were scored with Astrid Lindgren and Lund Childrens´Hospital Pain Scale for preterm infants (ALPS-0, validated, unpublished, score range 0-10) every 30 min and EDIN scale[21] every 4 h. All procedures were scored with PIPP.[22] Non-pharmacological and pharmacological pain treatment (morphine bolus, 0.15 mg/kg) was offered according to an algorithm based on pain scoring. A cerebral ultrasound was performed during the postintubation 24 h.

Outcome measures

The primary outcome measure was “good intubation conditions”, defined as a total intubation score of 10 or less, with all subitems scored 2 or less (Figure 1C).[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 h were secondary outcomes.

Analyzes

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

Physiological data were recorded at a sampling rate of 1Hz, and artifacts were manually excluded before data analysis. Median values of individual MABP, SpO_2, HR and $rScO_2$ were obtained from 1-min epochs at 5 time-points: before (baseline) and after drug administration; before starting intubation, directly after and 20 min after completed intubation. Median MABP and SpO_2 values were further calculated from 10-min epochs at 1, 2, 3 and 6 h after completed intubation. Individual changes in MABP, HR, SpO_2 and $rScO_2$ during the intubation procedure are expressed as median relative change (% change from baseline), and as the 90th percentile relative increase or decrease, representing the largest differences from baseline with exclusion of extreme values. Group data are expressed as mean (±SD). The duration of the respective increases and decreases in MABP, HR, SpO_2 and $rScO_2$ was taken into account by calculating the area under the curve (AUC; time x % change) for each variable. Median (IQR) values are given for non-normalized distributed parameters.

The aEEG trends were scored (EN and LHW) for continuity, sleep wake cycling, lower border of amplitude, bandwidth and the total sum of all subitems.[23] The classification was aided by inspection of the two-channel original EEG and performed in 1-h epochs for the first 6 h and for 3-h epochs thereafter.

Plasma cortisol concentrations were analyzed with a LC-MS/MS system equipped with an API 4000 triple quadrupole mass spectrometer (AB Sciex).[24]. Data were acquired and processed with the Analyst Software (Ver 1.4; AB Sciex).

Using SPSS 18.0 for Windows, Mann-Whitney, Fisher´s exact test, t-test and ANOVA were applied for statistic analyzes, as appropriate. A *P*-value <.05 was considered significant.

Results

In total 39 infants were randomized and 34 infants were included in the analysis, 17 in each study arm (Figure 1A). Of the 4 RSI infants who did not receive the allocated intervention, one infant received an accidental 10-fold overdose of thiopental[25] and was excluded from the study. Artifact-free aEEG-data were obtained for 14 infants in each group. No group differences were found at inclusion (Table1).

The primary outcome, "good intubation conditions", was significantly different between the RSI and morphine groups, 16/17 and 1/17 (P<.001), respectively. The median (IQR) intubation scores were 5 (5-6) vs 12 (10-13.5, *P*<.001). The total duration of the intubation procedure was shorter in the RSI group; 45 (35-154) vs 97 (49-365) s, (*P*=.031), as also the last intubation attempt; 40 (32-80) vs 60 (46-94) s, (*P*=.034) compared to the morphine group. However, the number of attempts needed 1 (1-1.5) and 1 (1- 2), did not differ. Additional drugs for intubation were given to 4 infants in the morphine group and none in the RSI group (*P*=.103, Fisher´s 2-sided exact test).

At baseline MABP, SpO_2, HR and $rScO_2$ values did not differ between the two allocation groups. During intubation, MABP increased and HR decreased significantly in the morphine group as compared to the RSI group, and a subsequent decrease in MABP occurred in the morphine group (Figure 2A and D). In the morphine group, the median (IQR) AUC increase in MABP was seven times larger; 690 (325-1180) vs 90 (0-270) in the RSI group (*P*=.005, Mann-Whitney), and the AUC of the HR decrease was five times larger; 3400 (1000-7700) vs 650 (480-1600), (*P*=.009). The MABP relative change during the intubation procedure from baseline was (mean±SD) a 21±23 % increase in the morphine and a 2 ±22% decrease in the RSI group (*P*=.007). There were no difference in median relative change, 90th percentile change or AUC decrease of SpO_2 and $rScO_2$ during the procedure. Volume expanders (saline, blood or plasma) were given within 2 hours prior to premedication, including three (one morphine and two RSI) infants who received a bolus saline infusion of 5 ml/kg before intubation. In total, 9 morphine and 11 RSI infants received a mean (SD) volume of 5.9 (6.0) and 7.0 (5.9) ml/kg, respectively, a non-significant difference. In ANOVA analyzes the following covariates did not change the significances in MABP and HR differences: the duration between termination of drug administration and intubation start, duration of intubation (total and for last attempt), number of attempts, volume expanders given two h before and extra doses of morphine after

the intubation. The RSI and morphine groups differed regarding MABP longitudinal changes calculated from the 1 min- and 10-min epochs from baseline to completed intubation, mean (SD) -2.48 (5.26) and 5.11 (7.35) (*P*=.002), and from completed intubation until 20 min -1.0 (5.41) and -9.16 (5.32), (*P*=.001), 1 h -1.87 (5.90) and -9.87 (9.02) (*P*=.008), 2 h -0.38 (7.02) and -11.65 (9.86) (*P*=.001), 3 h 1.7 (4.72) and -11.55 (10.97) (*P*<.001) and 6 h -2.23 (3.21) and -12.63 (9.26) (*P*=.001) later for the RSI and morphine groups, respectively. Compared to baseline, the postintubational decrease in MABP was significantly (*P*=.033) larger in the morphine group at 3 h; -6.44 (8.49) compared to -0.62 (5.92).

Plasma median (IQR) cortisol concentrations were similar in the RSI and morphine groups: 168 (37–324) and 183 (93–286) nmol/L at baseline, 185 (114-380) and 275 (152-357) at 20 min, 172 (79-299) and 240 (60-283) at 6 h and 142 (26-223) and 72 (46-187) at 24 h after the intubation. The pain scores were similar in RSI and morphine groups during the 6 h period post intubation; EDIN in all 1 vs 3, ALPS-0 ranged 1-2 vs 1-3, and PIPP 5-7 vs 2.5–7.5. Morphine boluses were given to five RSI infants (one received two doses and additional continuous infusion because of pneumothorax) at 1-6 h after the intubation. Six infants in the morphine group received bolus doses (one of them two doses) and additional infusions were administered to two other infants.

The neurophysiologic results differed significantly between the two interventions, with faster normalization in the RSI group and a prolonged central nervous depression in the morphine group up to 6 h after the intubation (Figure 3). One RSI infant had a pneumothorax and IVH after the intubation, with deterioration in EEG background activity.

Discussion

There has been increasing research interest in neonatal intubation premedication in recent years.[8, 9, 15, 26-33] Since our study start in 2005 several RCTs have been conducted,[27-30] but to our knowledge none has been performed on a balanced approach including sedatives, analgesics and muscle relaxants in newborns. Neither have the pharmacodynamic effects of short-acting drug combinations been investigated in this vulnerable population.

When using a combination of several drugs, it may be difficult to separate the effects of each drug. We consider possible differences between atropine and glycopyrrolate to be subtle or masked by the other drugs, since no previous publications indicate a difference and we did not find any HR differences after administration of the premedication. The significant group difference in procedural HR was most likely a result of optimal sedation and analgesia in RSI. However, individualized care of the infants resulted in similar $rScO_2$ and SpO_2 despite blood pressure decreases (Figure 2 B and C).

Using the traditional morphine premedication, a significant increase in MABP occurred during the intubation, which might be a sign of a pain/stress reaction. This was followed by a progressive decrease in MABP for 6 h. This morphine related MAPB decrease is in agreement with recently published data.[32] In placebo controlled RCT on newborn infants, thiopental was superior with shorter procedure duration and more stable hemodynamics.[7] We have studied postnatal pharmacokinetics and pharmacodynamics of thiopental, and found it suitable even for extremely preterm infants.[25, 34] Recently propofol, a short-acting sedative, has been suggested for newborns, since it provided good intubation conditions without muscle relaxants in a RCT.[28] However, in preterm infants, significant cerebral and systemic hypotensive effects may occur.[15, 35]

Remifentanil provided good intubation conditions and facilitated early extubation when used as monotherapy for INSURE,[30, 33]and was superior to morphine in a RCT.[29] No bradycardia or hypotension occurred with a dose less than 3 microg/kg.[30] As remifentanil is eliminated by nonspecific blood and tissue esterases into non-active metabolites independent of liver and renal function, it would theoretically be advantageous in preterm infants.[36] Fentanyl has a more rapid onset and a shorter duration of action than morphine, but longer duration than remifentanil.[10] Optimal premedication was reported with fentanyl in combination with muscle relaxants.[26, 27, 30, 31] There is a risk of chest wall rigidity after both fentanyl and remifentanil (3 microg/kg[30]) and a muscle relaxant must be added. Many new alternative relaxants are available[37] but the rapid onset, ultra-short acting suxamethonium without side effects, still justifies its role in RSI.[38]

Premedication with morphine was associated with a prolonged aEEG depression throughout the follow-up period, including more delayed onset of sleep wake cycling than in the RSI group. This should be interpreted as a considerable adverse effect. Observational studies have noted that both

opioids and phenobarbitone are associated with electrocortical background depression,[17, 18, 25] but no previous RCT has compared cerebral effects of morphine with those of the combination of thiopental and remifentanil.

Overall plasma cortisol levels were high in this preterm cohort [39] and the lack of significant changes in cortisol concentration to intubation can be explained by a high stress level at baseline without capacity to respond to further procedural stress/pain. The similar behavioral pain responses in both groups are probably a result of the individualized pain relief strategy, based on pain scores.

The major advantages of the RSI must be balanced against possible disadvantages of challenging drug prescription, preparation and administration with several drugs in a semi-urgent situation, recently high-lighted by Venkatesh et al.[32]. Medication errors are frequent, especially with drugs needing dilution,[25] and some could be avoided with neonatal formulations.

We aimed, in this RCT, to compare the traditional single-drug premedication with morphine to a more balanced approach with RSI. Difficulties in maintaining adequate mask ventilation in preterm patients during the required 10-15 min until peak-concentration and full effect of the morphine is of great importance and a major issue for creating other premedication strategies with short-onset drugs. Semi-urgent intubations of preterm infants in the NICU differ from non-urgent oral intubations before neonatal surgery, as they are predominately needed for respiratory failure in stressed and even exhausted infants with immature and restrictive lung parenchyma. Intubations may be complicated and interrupted by need for suctioning and mask-ventilation. Most intubation data are based on studies conducted with oral intubations, whereas we studied nasal intubations, the routine procedure in many NICUs. The time point of morphine administration at a minimum of 5.5 minutes prior to intubation was chosen with regard to this clinical problem, but can be considered a predictable shortcoming in addition to the case variability. The intubators, experienced neonatologists, were eight different persons that may be considered another study weakness.

An additional fluid bolus was administered to counteract a blood pressure drop, a well-known side-effect following administration of sedatives and analgesics in other populations. Though relevant for clinical purpose, this might have altered the impact of our results, but calculations showed a non-significant difference in administered volume between the groups.

Experimental data suggest that anesthetic drugs might have neurodegenerative effects on the developing rodent brain, and that combinations of drugs might generate more apoptosis than single drug therapy, however thiopental is considered safe as monotherapy in mice.[40] As all RSI drugs used are short-acting, the potential risks are probably small. Current trends in neonatal pain treatment recommend a "balanced approach" [5, 10] i.e. using appropriate amounts of drugs for adequate analgesia, but never more drugs than needed.

In conclusion, this RCT showed that RSI with rapid-onset short-acting thiopental and remifentanil provides clear benefits compared to morphine premedication: better intubation conditions and shorter procedure duration with less deviation in HR and MABP. The prolonged MABP decrease and aEEG depression after morphine premedication warrant us to recommend avoiding morphine for this indication. Given the modern gentle respiratory care, routine postintubation sedation and analgesia are not needed. Thus premedication drugs should have a rapid onset, short duration and be effective with few side-effects. Our RSI combination fulfilled these requirements and can be implemented in the clinic for preterm infants. However, a multidrug regimen always carries risks, and future research should aim at RCTs investigating new drugs with both sedative and analgesic effects.

Acknowledgements

We express our gratitude to the participating parents and infants, to the research nurses Ann-Cathrine Berg and Eva Hammarstrand, and the staff at the Neonatal Intensive Care Unit in Lund. We thank the safety committee Per Westrin, MD PhD, and Ulf Malmqvist, MD PhD, for their important support, and Per-Erik Isberg, PhD, Frank Wikström, PhD, and Lars-Johan Ahnlide, MSc, for statistical and technical support and Björn Larsson, MD, PhD, Baldvin Johnson, MD, PhD and Marie Olofsson, MD, for valuable discussions and collaboration. We thank Charlotte Casper, MD, PhD, and Mireille Vanpée, MD, PhD, for help with EDIN scale translation from French, and Agneta Kleberg, PhD, RN, and Pia Lundqvist, PhD, RN, for designing and validating the ALPS 0 scale.

References

1. Pokela ML, Koivisto M. Physiological changes, plasma beta-endorphin and cortisol responses to tracheal intubation in neonates. Acta Paediatr1994;83:151-6.
2. Duncan HP, Zurick NJ, Wolf AR. Should we reconsider awake neonatal intubation? A review of the evidence and treatment strategies. Paediatr Anaesth2001;11:135-45.
3. Perlman JM, McMenamin JB, Volpe JJ. Fluctuating cerebral blood-flow velocity in respiratory-distress syndrome. Relation to the development of intraventricular hemorrhage. N Engl J Med1983;309:204-9.
4. American Academy of Pediatrics CoFaNAAoP, Section of Surgery ; Canadian Paediatric Society; Fetus and Newborn Committee. Prevention and management of pain in the neonate. An update. Adv Neonatal Care2007;7:151-60.
5. Kumar P, Denson SE, Mancuso TJ. Premedication for nonemergency endotracheal intubation in the neonate. Pediatrics2010;125:608-15.
6. Barrington KJ, Finer NN, Etches PC. Succinylcholine and atropine for premedication of the newborn infant before nasotracheal intubation: a randomized, controlled trial. Crit Care Med1989;17:1293-6.
7. Bhutada A, Sahni R, Rastogi S, Wung JT. Randomised controlled trial of thiopental for intubation in neonates. Arch Dis Child d2000;82:F34-7.
8. Oei J, Hari R, Butha T, Lui K. Facilitation of neonatal nasotracheal intubation with premedication: a randomized controlled trial. J Paediatr Child Health2002;38:146-50.
9. Lemyre B, Doucette J, Kalyn A, Gray S, Marrin ML. Morphine for elective endotracheal intubation in neonates: a randomized trial [ISRCTN43546373]. BMC Pediatr2004;4:20.
10. Bottor LT. Rapid sequence intubation in the neonate. Adv Neonatal Care2009;9:111-7

11. Bohlin K, Jonsson B, Gustafsson AS, Blennow M. Continuous positive airway pressure and surfactant. Neonatology2008;93:309-15.

12. Hall RW, Kronsberg SS, Barton BA, Kaiser JR, Anand KJ. Morphine, hypotension, and adverse outcomes among preterm neonates: who's to blame? Secondary results from the NEOPAIN trial. Pediatrics2005;115:1351-9.

13. Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. Cochrane Database Syst Rev2003:CD002052.

14. van Alfen-van der Velden AA, Hopman JC, Klaessens JH, Feuth T, Sengers RC, Liem KD. Effects of midazolam and morphine on cerebral oxygenation and hemodynamics in ventilated premature infants. Biol Neonate2006;90:197-202.

15. Welzing L, Kribs A, Eifinger F, Huenseler C, Oberthuer A, Roth B. Propofol as an induction agent for endotracheal intubation can cause significant arterial hypotension in preterm neonates. Paediatr Anaesth2010;20:605-11.

16. van Bel F, Lemmers P, Naulaers G. Monitoring neonatal regional cerebral oxygen saturation in clinical practice: value and pitfalls. Neonatology2008;94:237-44.

17. Bell AH, Greisen G, Pryds O. Comparison of the effects of phenobarbitone and morphine administration on EEG activity in preterm babies. Acta Paediatr1993;82:35-9.

18. Shany E, Benzaquen O, Friger M, Richardson J, Golan A. Influence of antiepileptic drugs on amplitude-integrated electroencephalography. Pediatr Neurol2008;39:387-91.

19. Crawford MW, Hayes J, Tan JM. Dose-response of remifentanil for tracheal intubation in infants. Anesth Analg2005;100:1599-604.

20. Viby-Mogensen J, Engbaek J, Eriksson LI, Gramstad L, Jensen E, Jensen FS, et al. Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. Acta Anaesthesiol Scand1996;40:59-74.

21. Debillon T, Zupan V, Ravault N, Magny JF, Dehan M. Development and initial validation of the EDIN scale, a new tool for assessing prolonged pain in preterm infants. Arch Dis Child 2001;85:F36-41.

22. Stevens B, Johnston C, Petryshen P, Taddio A. Premature Infant Pain Profile: development and initial validation. Clin J Pain1996;12:13-22.

23. Burdjalov VF, Baumgart S, Spitzer AR. Cerebral function monitoring: a new scoring system for the evaluation of brain maturation in neonates. Pediatrics2003;112:855-61.

24. Turpeinen U, Stenman UH. Determination of urinary free cortisol by liquid chromatography-tandem mass spectrometry. Scand J Clin Lab Invest2003;63:143-50.

25. Norman E, Malmqvist U, Westrin P, Fellman V. Thiopental pharmacokinetics in newborn infants: a case report of overdose. Acta Paediatr2009;98:1680-2.

26. Dempsey EM, Al Hazzani F, Faucher D, Barrington KJ. Facilitation of neonatal endotracheal intubation with mivacurium and fentanyl in the neonatal intensive care unit. Arch Dis Child Fetal Neonatal Ed2006;91:F279-82.

27. Roberts KD, Leone TA, Edwards WH, Rich WD, Finer NN. Premedication for nonemergent neonatal intubations: a randomized, controlled trial comparing atropine and fentanyl to atropine, fentanyl, and mivacurium. Pediatrics2006;118:1583-91.

28. Ghanta S, Abdel-Latif ME, Lui K, Ravindranathan H, Awad J, Oei J. Propofol compared with the morphine, atropine, and suxamethonium regimen as induction agents for neonatal endotracheal intubation: a randomized, controlled trial. Pediatrics2007;119:e1248-55.

29. Pereira e Silva Y, Gomez RS, Marcatto Jde O, Maximo TA, Barbosa RF, Simoes e Silva AC. Morphine versus remifentanil for intubating preterm neonates. Arch Dis Child 2007;92:F293-4.

30. Choong K, AlFaleh K, Doucette J, Gray S, Rich B, Verhey L, et al. Remifentanil for endotracheal intubation in neonates: a randomised controlled trial. Arch Dis Child 2010;95:F80-4.

31. Lemyre B, Cheng R, Gaboury I. Atropine, fentanyl and succinylcholine for non-urgent intubations in newborns. Arch Dis Child 2009;94:F439-42.

32. Venkatesh V, Ponnusamy V, Anandaraj J, Chaudhary R, Malviya M, Clarke P, et al. Endotracheal intubation in a neonatal population remains associated with a high risk of adverse events. Eur J Pediatr2011;170:223-7.

33. Welzing L, Kribs A, Huenseler C, Eifinger F, Mehler K, Roth B. Remifentanil for INSURE in preterm infants: a pilot study for evaluation of efficacy and safety aspects. Acta Paediatr2009;98:1416-20.

34. Norman E, Westrin P, Fellman V. Placental transfer and pharmacokinetics of thiopentone in newborn infants. Arch Dis Child 2010;95:F277-82.

35. Vanderhaegen J, Naulaers G, Van Huffel S, Vanhole C, Allegaert K. Cerebral and systemic hemodynamic effects of intravenous bolus administration of propofol in neonates. Neonatology2009;98:57-63.

36. Welzing L, Ebenfeld S, Dlugay V, Wiesen MH, Roth B, Mueller C. Remifentanil degradation in umbilical cord blood of preterm infants. Anesthesiology2011;114:570-7.

37. Feltman DM, Weiss MG, Nicoski P, Sinacore J. Rocuronium for nonemergent intubation of term and preterm infants. J Perinatol2011;31:38-43.

38. Perry JJ, Lee JS, Sillberg VA, Wells GA. Rocuronium versus succinylcholine for rapid sequence induction intubation. Cochrane Database Syst Rev2008:CD002788.

39. Kajantie E, Raivio T, Janne OA, Hovi P, Dunkel L, Andersson S. Circulating glucocorticoid bioactivity in the preterm newborn after antenatal betamethasone treatment. J Clin Endocrinol Metab2004;89:3999-4003.

40. Fredriksson A, Ponten E, Gordh T, Eriksson P. Neonatal exposure to a combination of N-methyl-D-aspartate and gamma-aminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits. Anesthesiology2007;107:427-36.

Figures legends

Figure 1. Design of the study. Consort flow chart (A), intervention protocol (B) and intubation scoring (C) Morphine/saline placebo (syringe 1) was administered five min before the intubation, and the RSI drugs/saline placebo (syringes 2-5) during a one-min period, terminated minimum 30 s before the initiation of intubation (B). The Intubation score according to Viby-Mogensen was used (C).[21]

Figure 2. Results of physiological parameters.

Physiological data expressed as group mean (±SD) of individual median values from 1 min epochs at baseline (I), after premedication (II), before (III) and during the intubation (in green), as well as from 10 min epochs after (0-6 h) the intubation, in RSI (○) and morphine (●) groups.

During the intubation, the morphine group (■) had a larger heart rate (HR) increase[a] (26 % vs 8 %, P=.013) and decrease[b] (35% vs 18%, P =.012, panel A), and larger mean arterial blood pressure (MABP) increase[c] (38% vs 5%, P<.001, panel D) than the RSI group (□), mean (SD) of the 90th percentile values. Responses to intubation procedure were similar in $rScO_2$ (panel B) and SpO_2 (panel C). After the intubation MABP decreased in morphine infants and the group differences were significant at 2 and 3 hours, respectively (panel D).

Figure 3. aEEG total background score

The aEEG total background score (range 0-13, high score indicates normal cerebral activity) showed a continuous cerebral depression over the study period in the morphine group.

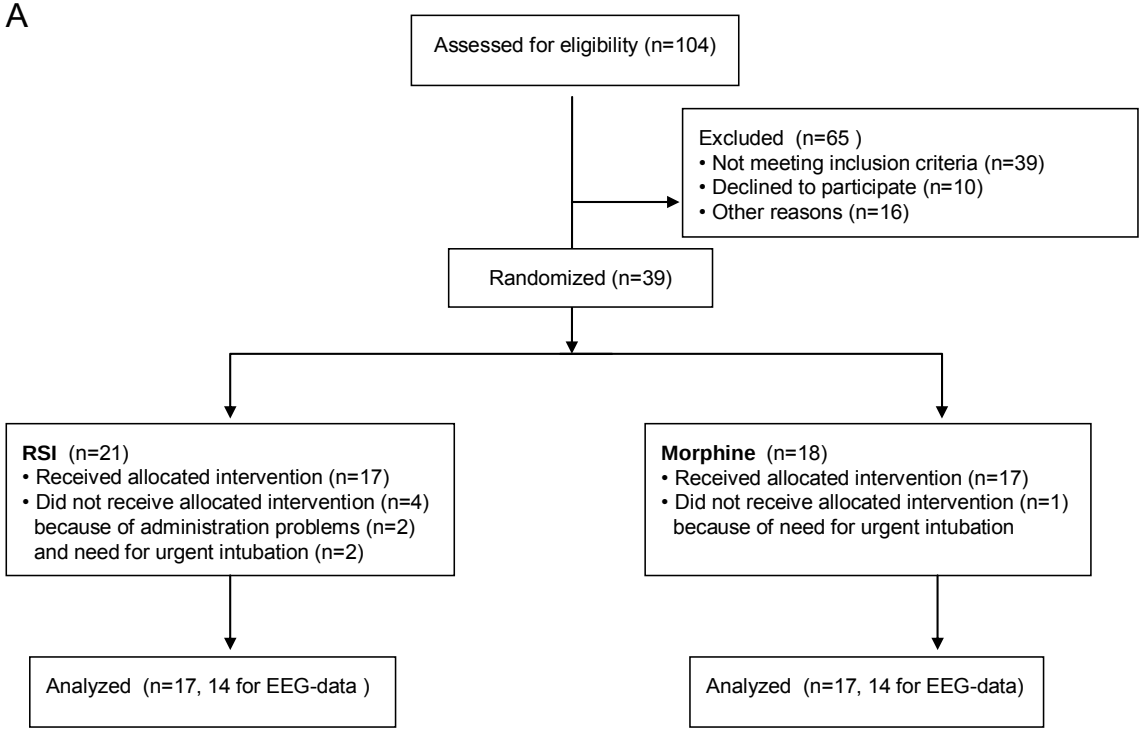
Table 1. Demographic and baseline clinical characteristics

	RSI (n = 17)	Morphine (n = 17)	Sign (*P*)
Stratification groups, n			
≤72 h and < 31 gw	7 (6)[a]	7 (6)[a]	ns
≤72 h and ≥ 31 gw	2 (1)[a]	2 (1)[a]	
>72 h and < 31 gw	8 (8)[a]	8 (8)[a]	
>72 h and ≥ 31 gw	0	0	
Male/female, n/n	11/6	9 / 8	ns
Gestational age at birth, wk	27.0 (25.6 – 28.5)	26.6 (25.1 – 28.7)	ns
Birth weight, g	925 (743 – 1220)	924 (721 – 1240)	ns
Postmenstrual age at intubation, wk	28.0 (26.9 – 29.8)	27.9 (26.1 – 29.0)	ns
Postnatal age at intubation, h	51 (26.5 – 281)	136 (17.5 – 322.5)	ns
Indication for intubation			
Respiratory distress syndrome	9	8	ns
Apnea	7	6	ns
Hemodynamically significant persistent ductus arteriosus	1	3	ns
Hemoglobin, g/L	144 (133 – 158)	145 (136 – 160)	ns
PCO_2, kPa	8.3 (7.3 – 10.0)	8.6 (7.9 – 10.0)	ns
CRP, mg/L	0.5 (0 – 2.9)	1.1 (0 – 4)	ns
Saline infusion or transfusion < 2h before intubation, ml/kg	10 (0 – 12)	6 (0 – 12)	ns
Plasma cortisol, nmol/L	168 (36.5 – 324.0)	183 (92.5 – 285.5)	ns
ALPS-0	3 (1-5)	4 (1.5 – 5.5)	ns
Intraventricular hemorrhage, *n*	3	3	ns

Numbers for cases with artefact-free aEEG (14 in each group) are given in brackets [a].

All values are in median and IQR.

A



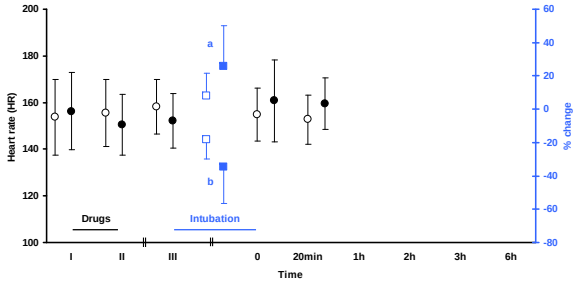
B

RSI	Time	Morphine
1. Saline	- 5 min	**1.** Morphine 0.3 mg/kg
2. Glycopyrrolate 5 microg/kg	- 1 min	**2.** Atropine 0.01 mg/kg
3. Thiopental 2 mg/kg < 1000g 3 mg/kg ≥ 1000g	- 45 s	**3.** Saline
4. Suxamethonium 2 mg/kg	- 30 s	**4.** Saline
5. Remifentanil 1 microg/kg	- 15 s	**5.** Saline
INTUBATION	**0** ≥ 30 s	INTUBATION

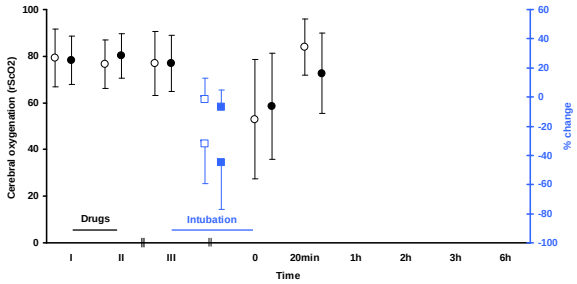
C

	1	2	3	4	Total
Laryngoscopy	Easy	Fair	Difficult	Impossible	
Vocal cords	Open	Moving	Closing	Closed	
Coughing	None	Slight	Moderate	Severe	
Jaw relaxation	Complete	Slight	Stiff	Rigid	
Limb movement	None	Slight	Moderate	Severe	
TOTAL					

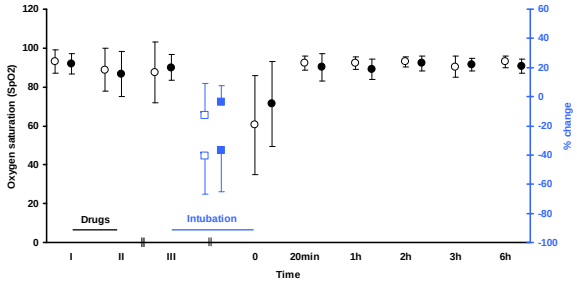
A


Heart rate (HR)
% change
a
b
Drugs
Intubation
I
II
III
0
20min
1h
2h
3h
6h
Time

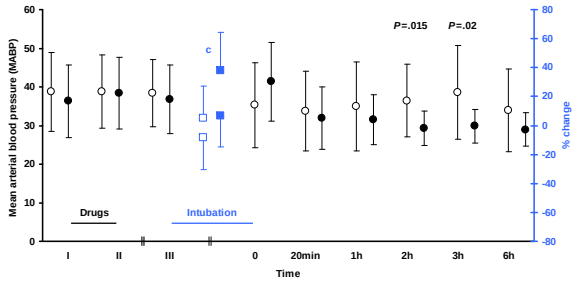
B

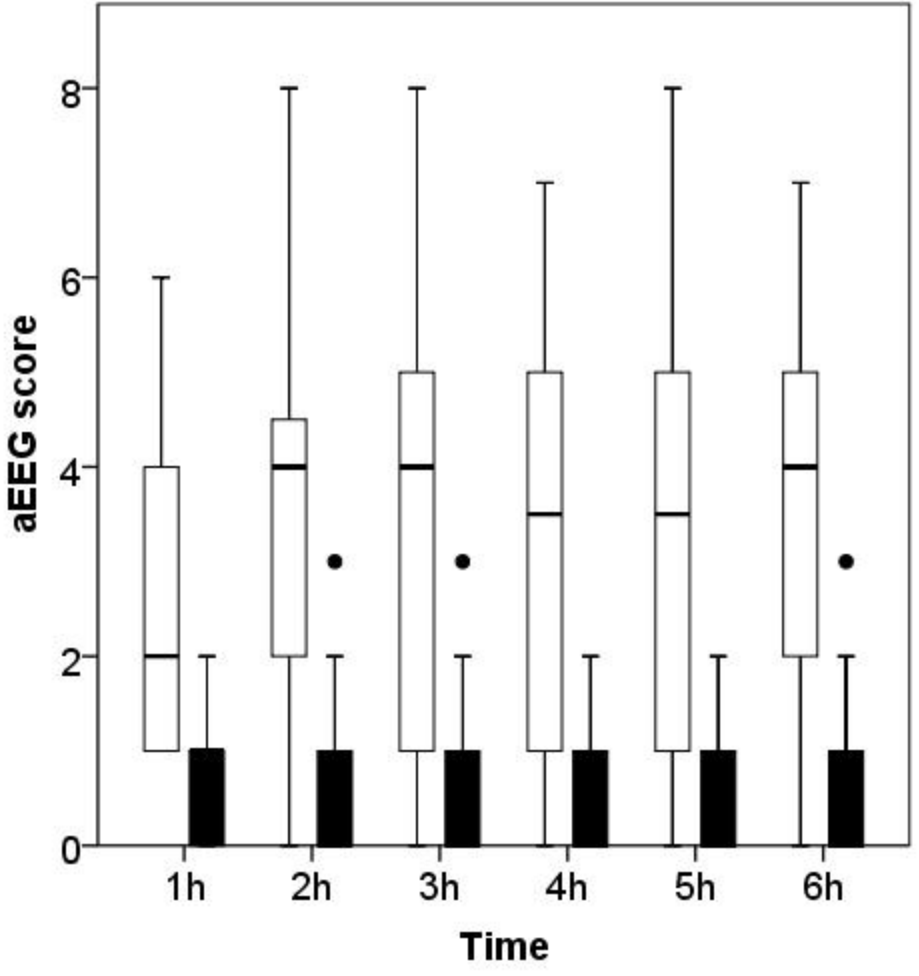

Cerebral oxygenation (rSc02)
% change
Drugs
Intubation
I
II
III
0
20min
1h
2h
3h
6h
Time

C


Oxygen saturation (SpO2)
% change
Drugs
Intubation
I
II
III
0
20min
1h
2h
3h
6h
Time

D


Mean arterial blood pressure (MABP)
% change
P=.015
P=.02
c
Drugs
Intubation
I
II
III
0
20min
1h
2h
3h
6h
Time


aEEG score
0
2
4
6
8
1h
2h
3h
4h
5h
6h
Time