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Premedication for intubation with morphine causes prolonged depression of electrocortical background activity in preterm infants

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ABSTRACT

Background: Sedative and analgesic medications are used in critically ill newborns, but little is known about their effects on electrocortical activity in preterm infants. We hypothesized that morphine might induce prolonged neurodepression, independent of blood pressure, compared with rapid sequence induction/intubation (RSI).

Methods: Of 34 infants enrolled into a randomized controlled trial (RCT) comparing RSI (including thiopental 2-3 mg/kg and remifentantil 1 microg/kg) with morphine (0.3 mg/kg) as premedication for intubation, 28 infants (*n*=14+14; median gestational age 26.1 weeks and postnatal age 138 h) had continuous two-channel amplitude-integrated electroencephalogram (aEEG/EEG) and blood pressure monitoring during 24 h after the intubation. Thirteen infants not receiving any additional medication constituted the primary study group. Visual and quantitative analyses of aEEG/EEG and blood pressure were performed in 3-h epochs.

Results: RSI was associated with aEEG/EEG depression lasting less than 3 h. Morphine premedication resulted in aEEG/EEG depression with more discontinuous background and less developed cyclicity for 24 h, and during the first 9 h interburst intervals were significantly increased compared to RSI. The difference was not related to blood pressure.

Conclusion: Premedication with morphine is associated with prolonged aEEG/EEG depression independent of blood pressure changes, and may not be optimal for short procedures.

INTRODUCTION

Sedative and analgesic medications are commonly needed in preterm and term infants during neonatal intensive care. Many of these drugs are known to cause cerebral depression (1-6) and also arterial hypotension with potentially compromising cerebral side-effects, especially in preterm infants (7-9). Only a few prospective studies have systematically evaluated drug effects on the electroencephalogram (EEG) in newborn infants (2, 5, 6, 10, 11). Since amplitude integrated EEG (aEEG) and EEG monitoring is increasingly used in neonatal intensive care units (NICU) (12), drug effects on neonatal aEEG/EEG should be characterized in relation to gestational age (GA).

Endotracheal intubation is considered to be very painful and is associated with acute increases in blood pressure and intracranial pressure, with bradycardia and hypoxia (13, 14), and with a risk of neurological complications (15). Current recommendations emphasize that elective and semi-urgent intubations in infants should be performed after premedication (16, 17). In newborns, morphine is still frequently used despite it´s slow onset and long duration of action (17, 18). Recently we demonstrated, in a randomized controlled trial (RCT) including preterm infants, that the intubation conditions were improved and the acute hemodynamic effects (heart rate and mean arterial blood pressure, MABP) on the infant were significantly milder after premedication with short-acting analgo-sedation including thiopental, remifentanil and muscle relaxation (so called rapid sequence induction/intubation, RSI) versus morphine (19). The advantages of short-acting analgo-sedation before intubation of newborn infants have previously been reported in a few other RCTs (13, 20-22).

The current study is a secondary analysis of our RCT (19) comparing electrocortical and blood pressure responses of the RSI strategy and premedication with morphine over 24 h. We hypothesized that morphine administration would cause a more pronounced aEEG/EEG depression independent of blood pressure compared to RSI.

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RESULTS

aEEG scores

The premedication effect on the Burdjalov total aEEG scores was significantly different between the treatments when no additional medication was given. The scores were lower for all 3-h epochs of the 24-h study period in the five morphine infants compared to the eight infants receivning only RSI (*P*-values ranging between 0.003 and 0.018), Figure 1A. In the 15 infants who received additional doses of morphine, there were no significant differences in Burdjalov total scores between the two randomization groups. For the total group of 14+14 infants, the Burdjalov total scores were significantly lower in the morphine group than in the RSI group in 5 of the 3-h epochs, and for the other epochs borderline significances between the groups were obtained.

Sleep wake cycling was not found during the 24 h study period in any of the morphine infants who only received premedication, while 5 of the 9 infants in the RSI group had developed at least imminent cyclicity during the first 3-h epoch after the intubation. The SWC subscores were significantly lower in the morphine group for all 3-h epochs during the study period (*P*-values 0.002 to 0.014). In the 15 infants who received additional morphine, the SWC scores only differed between the two randomization groups during the first 6 h (*P*-values 0.001 and 0.002), whereas the SWC scores differed during all 3-h epochs in the total study group.

The BG-scores were significantly lower after morphine premedication compared to RSI for all 3-h epochs during the study period with a median score of 2 for all epochs in the morphine group (i.e. burst suppression dominating) and ranging between 7.5 and 8.5 (i.e. mainly continuous background) in the RSI group (*P*-values 0.003 to 0.017), Figure 1B. When additional morphine doses were given after intubation, the RSI infants were not significantly different than the morphine group. In the total study group, the BG-scores were also significantly lower in the morphine group versus the RSI group for all 3-h epochs during the study period.

Interburst intervals (IBI) and interburst percentage (IB%)

In infants with morphine premedication, the IBI and IB% differed significantly from RSI treated infants during the first 9 h, Figures 1C and 1D. This group difference was not found when the infants had received additional morphine doses after intubation. In the total study group, the IBIs were significantly prolonged and IB% was higher in the morphine group as compared to the RSI group during the first 6 h after the intubation.

Statistical adjustment for postnatal age (PNA) (23) did not change the IBI results, whereas IB% values were clearly dependent on PNA throughout the whole study period (0-24 h). Adjustment for the infants´ actual weight at study entry was also performed since the thiopental dose in the RSI group varied according to the infants weight, however this did not change the IBI or IB% results.

Electrographic seizures were detected in three infants; one infant in the RSI group had a brief seizure 6 h after the intubation and this infant also had an IVH grade I. Two infants in the morphine group had repeated subclinical seizures without IVHs at 0-9 h and 15-24 h, and at 3-12 h, respectively, after the intubation. None of these infants had IVHs and both infants had uneventful intubations. These three infants did not differ from the other infants in any other aspect.

Effects of additional bolus doses of morphine

Transient aEEG/EEG depression was frequently seen after morphine boluses, Figure 2. Eight infants, four in each randomization group, received a single additional bolus dose of morphine according to an algorithm based on pain score results. Compared to the baseline during 1 h before the bolus, the IBIs were significantly prolonged at 2-3 h and at 3-4 h after the bolus (*P*-values 0.012 and 0.012, respectively), while IB% continued to be increased 6 h after the bolus (*P*-values between 0.012 and 0.028 for all six 1-h epochs, compared to baseline), Figure 3. There were no differences in this response between the two randomization groups.

Blood pressure

In the infants who only received the premedication, MABP differed significantly or near significantly (*P*-values ranging from 0.028 to 0.123) for all 3-h epochs during the study period, with lower MABP in the infants allocated to morphine, Table 1. The randomization groups in the whole study population did not differ as regards MABP. Univariate analysis of variance of all 28 infants demonstrated that the main effects on aEEG/EEG differences (Burdjalov total score and SWC; BG-score) between the two groups were due to group allocation (*P*=0.002-0.049). However, a major influence from MABP explained significant differences in the aEEG/EEG scores between the two randomization groups at 6-9 h and 15-24 h. This blood pressure influence on aEEG/EEG differences disappeared when only the 13 infants who did not receive additional doses of morphine were compared.

DISCUSSION

The main finding in this study was that administration of morphine is associated with prolonged neurodepression and decreased blood pressure in very preterm infants. Twenty-four hours after a loading dose of morphine, electrocortical activity remained significantly depressed with lack of sleep wake cycling. The electrocortical depression occurred independently of the blood pressure response. In our RCT, morphine premedication was associated with more pronounced aEEG/EEG depression and acute circulatory changes during and after intubation than the RSI combination of thiopental and remifentanil (19). However, prolonged effects of these premedications have not been studied in very preterm infants in a randomized study.

Neonatal intensive care today is increasingly “brain oriented”. Preterm infants need intensive care treatment during a vulnerable period with an immature but rapidly developing central nervous system. The increased risks for circulatory and neurodepressive side-effects from sedatives and opioids are acknowledged as well as the potentially dangerous effects of the drugs on the developing brain, and currently a “balanced approach” is recommended i.e. administration of appropriate amounts of drugs to provide adequate analgesia, but never more drugs than needed. Such strategies are best achieved with systematic pain assessment and adequate pain treatment based on pharmacokinetic and pharmacodynamic studies (24).

Considering the current knowledge on morphine effects in preterm infants, the premedication dose of morphine in our RCT, 0.3 mg/kg, is high (21) and is considered a study weakness. At the time when the study was designed, the dose was chosen to meet the clinical need for a semi-urgent intervention referring to a previous study which showed that a moderately high dose of morphine, 0.2 mg/kg, had no positive effects compared to placebo (25). In our trial, additional doses of morphine, 0.15 mg/kg, were administered in both randomization groups as indicated according to validated pain scales. Our data clearly demonstrated that the most prominent differences in electrocortical and blood pressure responses between the randomization groups were related to the assigned premedication, underscoring the risk of prolonged neurodepressive effect of a single high bolus dose of morphine. However, although in a limited number of infants, the EEG remained depressed for more than six hours after a smaller single dose of morphine irrespective of which premedication was used.

Similar effects on aEEG/EEG from single doses of morphine and other opioids have been reported by other investigators. Bell and Greisen noted significantly prolonged IBIs in very preterm infants lasting up to 5-6 h after a single dose of morphine (0.1-0.2 mg) and up to 11-12 h if diazepam (0.5-1 mg/kg) had been administered previously (1). Young and da Silva demonstrated EEG background depression and presence of excessive epileptiform activity (but no seizures) during morphine infusion, which resolved when the morphine was discontinued (10). A recent Dutch study of preterm infants with respiratory distress syndrome reported prolonged electrocortical depression in infants who were briefly intubated to receive surfactant after premedication with morphine (0.1 mg/kg) which was reversed with naloxone, in contrast to infants who were treated with continuous positive airway pressure (CPAP) and did not receive morphine (5). The reason for the long-standing aEEG depression was not obvious. The study was not randomized, and the aEEG depression may have been attributed to greater illness severity in the group who needed intubation or to a more rapid turnover of naloxone, with morphine effects persisting after naloxone reversal. Bolus doses of other opioids, sufentanil or fentanyl, can also induce profound and prolonged EEG depression in both preterm and term infants (2, 6). Sleep pattern is altered with reduced REM sleep after oxycodone administration (26), which is consistent with our results on depressed SWC after morphine administration. The present data demonstrate that a single dose of remifentanil, in combination with thiopental, is associated with a short electrocortical depression lasting less than three hours in very preterm infants. There are no previous reports on EEG responses to remifentanil in newborns, and with the current study design it was not possible to differentiate the effects of remifentanil and that of thiopental. Currently available information on remifentanil effects in preterm infants is consistent with ours, and this drug seems promising in several aspects for the use in short NICU procedures (24).

The effects of morphine on MABP in preterm infants during mechanical ventilation have been investigated in two large RCTs with diverging results (7, 27). In the current study, the morphine group tended to have lower MABP than the RSI group, which was most evident with significant or near-significant differences for all 3-h epochs when the two premedication strategies were compared in infants who did not receive additional doses of morphine. The present data also demonstrate that MABP affected aEEG/EEG independently of randomization group, which is in accordance with findings in a few other studies. Minor changes in aEEG amplitudes have been associated with blood pressure changes during blood exchange transfusion (28). Further, enhanced blood pressure in hypotensive preterm infants was associated with increased burst rates or decreased IBI in some, but not in all, infants (11, 29). In very preterm infants, multiple correlations were found between the EEG variables continuity and amplitude versus blood pressure and right ventricular flow output (30).

Subclinical seizures were detected in the aEEG/EEG registration of three infants (11% of the study cohort). Few studies have reported a possible association between morphine and epileptiform activity and seizures (10, 31), and that two infants developed subclinical seizures of several hours' duration in conjunction with morphine administration should be considered a major concern. The mechanism of morphine-derived seizures in preterm infants is unknown; a possible explanation might be that μ-opioid receptor-mediated analgesia is GABA dependent, and that GABA acts as an excitatory transmitter in early postnatal life (32, 33). A potential association between epileptic activity and morphine in preterm infants should be investigated in future studies. Continuous aEEG is becoming routine monitoring in many NICUs, especially in very sick infants, and consequently we will gain more information of the cortical activity and potential seizures in infants receiving morphine infusions and other drugs that might give cerebral side-effects.

The lack of aEEG/EEG baseline data before the intubation is a limitation in our study. All infants needed semi-urgent intubation and we considered that applying EEG electrodes in this situation would imply further unacceptable stress and possible time delay. Another limitation is the small number of patients that constituted the primary study population, the 13 infants who did not receive additional analgesics or sedatives after the premedication. The power analysis of the primary outcome of the RCT was based on an estimated 30% improvement in good intubation condition assessed with an intubation score using RSI (19), and was not applicable for this secondary analysis.

In conclusion, our data show that morphine administration in very preterm infants is associated with prolonged cerebral depression, more discontinuous aEEG/EEG background pattern and lack of sleep wake cycling persisting for 24 hours. In contrast, RSI premedication with thiopental and remifentanil resulted in shorter EEG depression and less blood pressure changes in addition to the advantage of better intubation conditions with less effect on acute physiological parameters (19). Commonly used analgesic doses of morphine also had a neurodepressive effect lasting at least 6 h. Thus, drug effects must be considered when diagnostic EEGs are performed for assessment of brain function. The use of morphine premedication should be questioned in favor of short-acting sedatives and analgesics for short procedures in the NICU.

PATIENTS AND METHODS

The study was carried out at the tertiary level NICU at Lund University Hospital, Lund, Sweden. The Regional Ethics Committee in Southern Sweden and the Medical Products Agency in Sweden approved the research protocol, registered as EudraCT no 2004-001583-52 and at www.clinicaltrials.gov no NCT00216944. Written informed consent was obtained from both parents before enrolment. The study protocol and all the analyses were carried out blindly (19).

Patients

Inclusion criteria in the RCT were as follows; need for semi-urgent intubation (due to e.g. respiratory distress syndrome, patent ductus arteriosus or sepsis), prematurity with GA less than 37 weeks and no analgesic or sedative drugs administered during the previous 24 hours (h). Exclusion criteria were; birth asphyxia (Apgar score <4 at 10 min or an umbilical cord pH <7.0), serum potassium > 6 mmol/L, major malformations and postoperative care. Of the original 39 infants that were randomized, 28 infants with a GA less than 32 weeks had a complete aEEG registration for 24 h and were included in this study, Figure 4. The clinical characteristics did not differ between the two allocation groups, Table 2. Intraventricular hemorrhages (IVH) were diagnosed in 5 infants before study entry. One infant in the RSI group developed an IVH grade 1 during the study period in association with a pneumothorax.

Study protocol

The infants were randomized to receive either RSI i.e. a combination of glycopyrrolate (5 µg/kg), thiopental (2 mg/kg if the weight was < 1000g, 3 mg/kg if ≥ 1000g), suxamethonium (2 mg/kg) and remifentanil (1 µg/kg), or atropine (0.01 mg/kg) and morphine (0.3 mg/kg) as premedication before semi-urgent intubation, and were monitored during a 24 h follow-up study period. Pain/stress was scored every 30 min using two validated pain scales (the Echelle Douleur Inconfort Nouveau-ne, EDIN, and the Astrid Lindgren and Lund childrens´ hospitals Pain assessment Scale for premature infants, ALPS-0) for continuous stress/pain. Additional analgesic treatment (bolus doses of morphine, 0.15 mg/kg) was administered if pain/stress was present according to an algorithm based on the pain scoring (19). In total 15 of the 28 infants with aEEG/EEG recordings received 1 to 4 (median 1, no difference between randomization groups) additional doses of morphine, 6 infants in the RSI group and 9 infants in the morphine group. Three of these infants (one in the RSI group and two in the morphine group) required morphine infusions (10-13 μg/kg/h). One infant in the morphine group also received diazepam (0.1 mg/kg) at intubation, otherwise no additional medications with known effects on electrocortical activity or blood pressure were administered. Thirteen infants, 8 in the RSI group and 5 in the morphine group, received only the allocated premedication, Figure 4.

A two-channel electroencephalogram (EEG) with the amplitude-integrated EEG trend (aEEG/EEG) was recorded (Nervus Monitor 1.3, Taugagreining HF, Reykjavik, Iceland/Nicolet monitor, Care Fusion, Madison, WI, USA) continuously after the intubation, starting 20 min after completed procedure. Hydrogel electrodes (Ambu® Neuroline, Ambu A/S, Ballerup, Denmark) were applied after gentle skin preparation with NUPREP® cream (GRASS Technologies, West Warwick, USA) for recording from bilateral derivations (F3-P3, F4-P4 with a reference at Cz according to the International 10-20 system). Heart rate, MABP and oxygen saturation were continuously (second-to-second) recorded (HEWLETT-PACKARD Monitor M1094A/ M1166A, HP Sweden, Kista, and Nellcor N395 PulseOximeter, Nellcor Puritan Bennett Inc, Pleasanton, USA) from baseline before the premedication and data were transferred to the Nervus/Nicolet monitor for concomitant data processing, Figure 2. In addition to that, near NIRS (Near infrared spectroscopy) monitoring was performed during the period of drug administration and intubation and the following 20 minutes. A cerebral ultrasound was performed 24 h after intubation in all infants (19).

Data analyses

Electrophysiological analyses

Visual classification of the aEEG trend was performed according to Burdjalov (34). The tracings were scored during 3-h epochs for continuity (scores 0-2), sleep wake cycling (SWC: scores 0-5), lower border of amplitude (scores 0-3), bandwidth (scores 0-4), and the total sum of all subscores (0-13; higher scores indicating more active cerebral activity). In addition, the dominating electrocortical background pattern (BG) was also scored for each 3-h epoch with the use of the original EEG, according to a modified pattern classification system, BG-score: score 10: 100% continuous (C); score

9: 75% C and 25% discontinuous (DC, i.e. preterm tracé discontinue, but not burst suppression, BS); score 8: 50% C and 50% DC; score 7: 25% C and 75% DC; score 6: 100% DC; score 5: 75% DC and 25% BS; score 4: 50% DC and 50% BS; score 3: 25% DC and 75% BS; score 2: 100% BS; score 1: sparse BS with <100 bursts/h (BS-) or inactive (35). The aEEG/EEG background was scored by two assessors together (EN and LWH). Suspected seizures in the aEEG trace were verified (or invalidated) by inspection of the EEG by a clinical neurophysiologist (IR).

Secondly, quantitative analysis of EEG background continuity was performed over 3-h epochs by semi-automated measurements of the duration of the interburst intervals (IBI) and interburst percentage (IB%, i.e. percentage of recording detected as IBI). The IBIs were detected with a recently validated segmentation algorithm (36), with software available in the Nervus/Nicolet monitor and based on a Non Linear Energy Operator, reflecting both amplitude and frequency content of the EEG (37). Before automated detection, the aEEG trend and original EEG was inspected for ongoing interference and seizures, which were excluded from analysis (SW).

To assess the effect of a single bolus dose of morphine on the EEG, the IBI and IB% were averaged 1-hourly from 1 h before until 6 h after the bolus. This analysis was performed in eight infants fulfilling the following criteria: at least 12 h since intubation medications, no additional morphine during the following 6 h after the bolus and sufficient EEG quality for quantitative analysis.

Blood pressure

Invasive MABP from umbilical or peripheral arterial catheters, inserted on clinical indication, was continuously sampled at 1 s resolution. Artifacts were manually excluded before data analysis. One h of MABP data from the middle 1-h segment of each 3-h period during the 24 h study period was averaged over 4-s epochs.

Statistical analysis

SPSS version 18.0 was used for statistical analyses. Non-parametric and parametric statistics were applied as appropriate and included Mann-Whitney U-test, Wilcoxon signed ranks test, Student´s t-test and univariate ANOVA and ANOVA with repeated measurements. A P-value < 0.05 was considered significant.

The data were analyzed with regard to the randomization allocation, but with the primary objective to investigate the premedication effect, separate analyses of the aEEG/EEG and blood pressure reactions were performed also for the subgroups of the 13 infants who received only the premedication and the 15 infants who received additional sedative or analgesic medications during the study period, Figure 4.

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REFERENCES

1. Bell AH, Greisen G, Pryds O. Comparison of the effects of phenobarbitone and morphine administration on EEG activity in preterm babies. Acta Paediatr 1993;82:35-9.
2. Nguyen The Tich S, Vecchierini MF, Debillon T, Pereon Y. Effects of sufentanil on electroencephalogram in very and extremely preterm neonates. Pediatrics 2003;111:123-8.
3. Herbertz S, Pulzer F, Gebauer C, Panhofer M, Robel-Tillig E, Knupfer M. The effect of maturation and sedation on amplitude-integrated electroencephalogram of the preterm neonate: results of a prospective study. Acta Paediatr 2006;95:1394-9.
4. Shany E, Benzaquen O, Friger M, Richardson J, Golan A. Influence of antiepileptic drugs on amplitude-integrated electroencephalography. Pediatr Neurol 2008;39:387-91.
5. van den Berg E, Lemmers PM, Toet MC, Klaessens JH, van Bel F. Effect of the "InSurE" procedure on cerebral oxygenation and electrical brain activity of the preterm infant. Arch Dis Child Fetal Neonatal Ed 2010;95:F53-8.
6. Bernet V, Latal B, Natalucci G, Doell C, Ziegler A, Wohlrab G. Effect of sedation and analgesia on postoperative amplitude-integrated EEG in newborn cardiac patients. Pediatr Res 2010;67:650-5.
7. 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. Pediatrics 2005;115:1351-9.
8. Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. Cochrane Database Syst Rev 2003:CD002052.
9. 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 Neonate 2006;90:197-202.
10. Young GB, da Silva OP. Effects of morphine on the electroencephalograms of neonates: a prospective, observational study. Clin Neurophysiol 2000;111:1955-60.
11. Victor S, Marson AG, Appleton RE, Beirne M, Weindling AM. Relationship between blood pressure, cerebral electrical activity, cerebral fractional oxygen extraction, and peripheral blood flow in very low birth weight newborn infants. Pediatr Res 2006;59:314-9.
12. Boylan G, Burgoyne L, Moore C, O'Flaherty B, Rennie J. An international survey of EEG use in the neonatal intensive care unit. Acta Paediatr 2010;99:1150-5.

13. Pokela ML, Koivisto M. Physiological changes, plasma beta-endorphin and cortisol responses to tracheal intubation in neonates. Acta Paediatr 1994;83:151-6.
14. Duncan HP, Zurick NJ, Wolf AR. Should we reconsider awake neonatal intubation? A review of the evidence and treatment strategies. Paediatr Anaesth 2001;11:135-45.
15. 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 Med 1983;309:204-9.
16. 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 Care 2007;7:151-60.
17. Kumar P, Denson SE, Mancuso TJ. Premedication for nonemergency endotracheal intubation in the neonate. Pediatrics 2010;125:608-15.
18. Kelleher J, Mallya P, Wyllie J. Premedication before intubation in UK neonatal units: a decade of change? Arch Dis Child Fetal Neonatal Ed 2009;94:F332-5.
19. Norman E, Wikstrom S, Hellstrom-Westas L, Turpeinen U, Hamalainen E, Fellman V. Rapid Sequence Induction is Superior to Morphine for Intubation of Preterm Infants: A Randomized Controlled Trial. J Pediatr 2011;159:893-9.
20. 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. Pediatrics 2006;118:1583-91.
21. 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 Fetal Neonatal Ed 2007;92:F293-4.
22. Choong K, AlFaleh K, Doucette J, et al. Remifentanil for endotracheal intubation in neonates: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2010;95:F80-4.
23. West CR, Harding JE, Williams CE, Gunning MI, Battin MR. Quantitative electroencephalographic patterns in normal preterm infants over the first week after birth. Early Hum Dev 2006;82:43-51.
24. Allegaert K. The clinical pharmacology of short acting analgo-sedatives in neonates. Curr Clin Pharmacol 2011;6:222-6.
25. Lemyre B, Doucette J, Kalyn A, Gray S, Marrin ML. Morphine for elective endotracheal intubation in neonates: a randomized trial [ISRCTN43546373]. BMC Pediatr 2004;4:20.

26. Axelin A, Kirjavainen J, Salantera S, Lehtonen L. Effects of pain management on sleep in preterm infants. Eur J Pain 2010;14:752-8.
27. Simons SH, Roofthooft DW, van Dijk M, et al. Morphine in ventilated neonates: its effects on arterial blood pressure. Arch Dis Child Fetal Neonatal Ed 2006;91:F46-51.
28. Benders MJ, Meinesz JH, van Bel F, van de Bor M. Changes in electrocortical brain activity during exchange transfusions in newborn infants. Biol Neonate 2000;78:17-21.
29. Greisen G, Pryds O, Rosen I, Lou H. Poor reversibility of EEG abnormality in hypotensive, preterm neonates. Acta Paediatr Scand 1988;77:785-90.
30. West CR, Groves AM, Williams CE, et al. Early low cardiac output is associated with compromised electroencephalographic activity in very preterm infants. Pediatr Res 2006;59:610-5.
31. Koren G, Butt W, Chinyanga H, Soldin S, Tan YK, Pape K. Postoperative morphine infusion in newborn infants: assessment of disposition characteristics and safety. J Pediatr 1985;107:963-7.
32. Cherubini E, Gaiarsa JL, Ben-Ari Y. GABA: an excitatory transmitter in early postnatal life. Trends Neurosci 1991;14:515-9.
33. Christie MJ, Connor M, Vaughan CW, Ingram SL, Bagley EE. Cellular actions of opioids and other analgesics: implications for synergism in pain relief. Clin Exp Pharmacol Physiol 2000;27:520-3.
34. Burdjalov VF, Baumgart S, Spitzer AR. Cerebral function monitoring: a new scoring system for the evaluation of brain maturation in neonates. Pediatrics 2003;112:855-61.
35. Hellstrom-Westas L, Rosén I, de Vries LS, Greisen G. Amplitude-integrated EEG. Classification and Interpretation in Preterm and Term Infants. NeoReviews 2006; 7(No 2).
36. Palmu K, Wikstrom S, Hippelainen E, Boylan G, Hellstrom-Westas L, Vanhatalo S. Detection of 'EEG bursts' in the early preterm EEG: visual vs. automated detection. Clin Neurophysiol 2010;121:1015-22.
37. Palmu K, Stevenson N, Wikstrom S, Hellstrom-Westas L, Vanhatalo S, Palva JM. Optimization of an NLEO-based algorithm for automated detection of spontaneous activity transients in early preterm EEG. Physiol Meas 2010;31:N85-93.

FIGURE LEGENDS

Figure 1. aEEG/EEG data of infants with no additional analgesics after intubation

The Burdjalov, total scores (panel A) and BG-scores (panel B) differed significantly between the 8 RSI (checkered black and white) and 5 morphine (white) infants during 24 h. During the first three periods both IBI (panel C) and IB% (panel D) differed significantly.

The level of significance is indicated by * $P<0.01$ and ** $P<0.05$

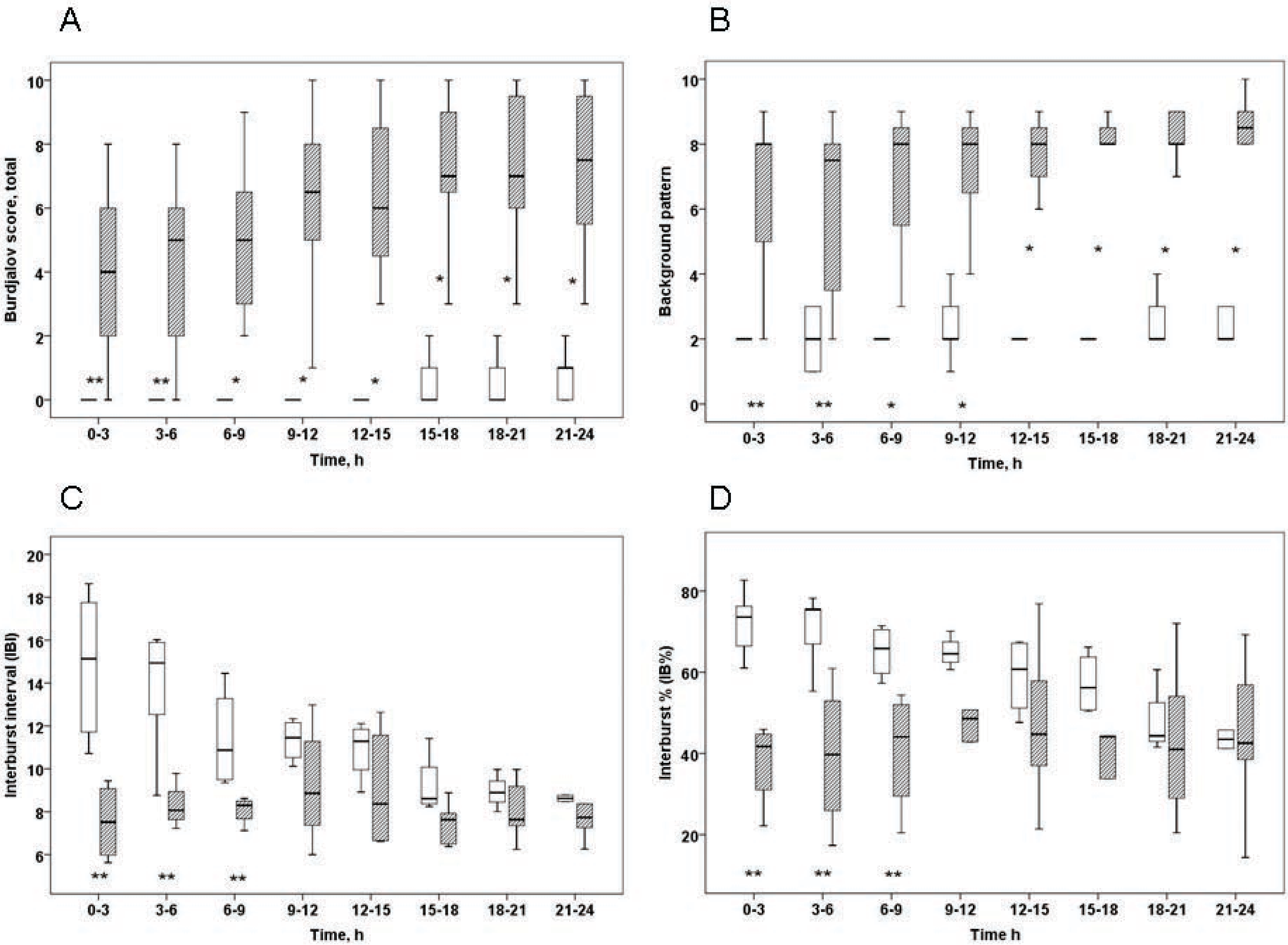
Figure 2. Study monitor with an example of a morphine bolus effect

A recording with time-synchronized two-channel EEG/aEEG, MABP and oxygen saturation (SpO_2, plethysmography), showing a reaction in aEEG and MABP trends from a single bolus dose of morphine (arrow to the left) in a very preterm infant. The three upper traces show 4-h aEEG (left and right electrodes) and MABP trends, and below 25 seconds of EEG (left and right electrodes), MABP and saturation (SpO_2). The lower border of the F3-P3 aEEG trace is distorted by an addition of an artifact induced by high frequency ventilation, started at 02.50. The arrow to the right marks the onset of high-frequency ventilation, resulting in an artefact that lifts the aEEG trace.

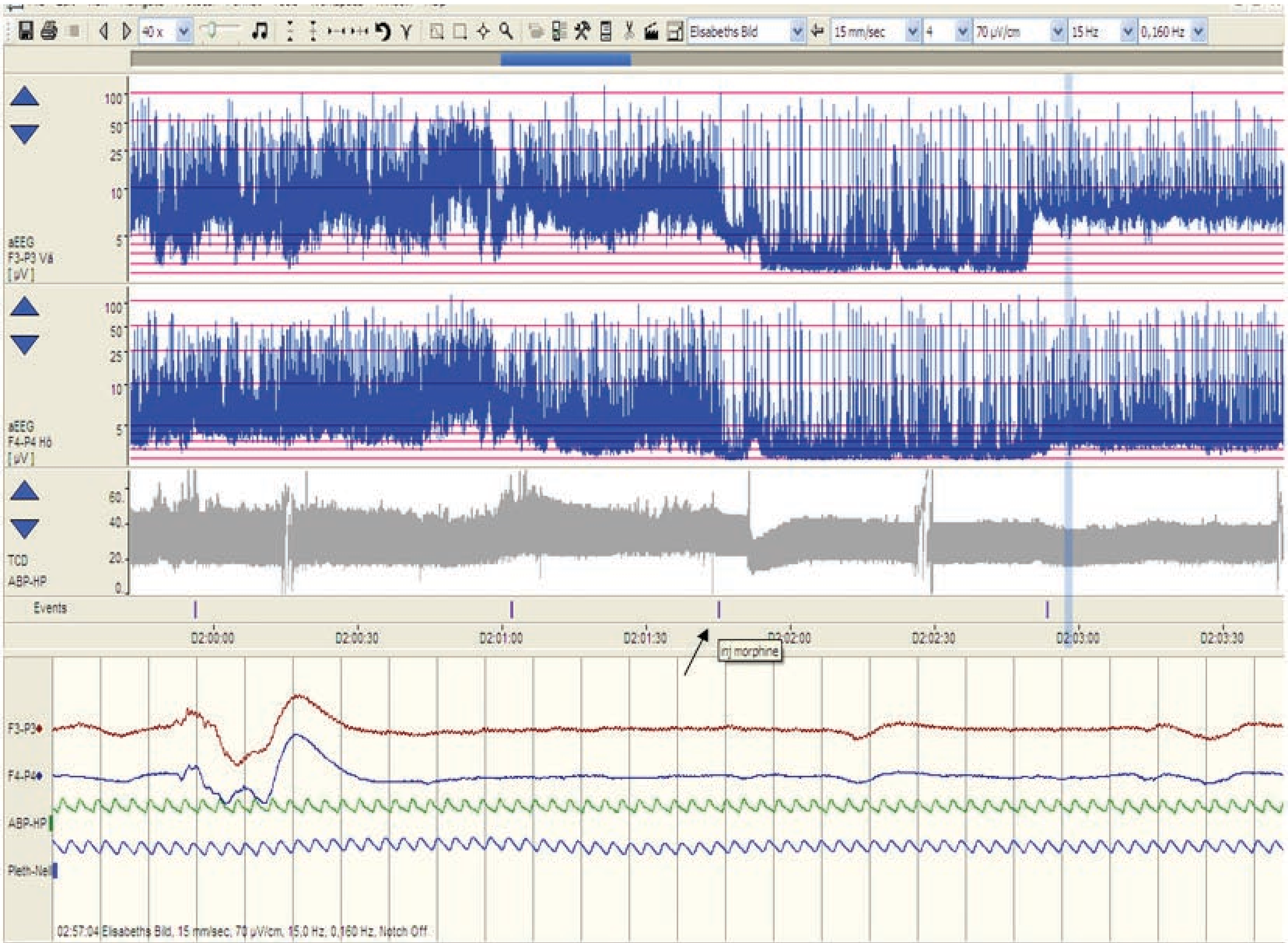
Figure 3. Quantitative data of single doses of morphine

IBI (panel A) and IB% (panel B) were quantified in 1-h epochs up to six hours after a single bolus dose of morphine, 0.15 mg/kg, administered to four RSI infants (whole lines) and four morphine infants (dotted lines).

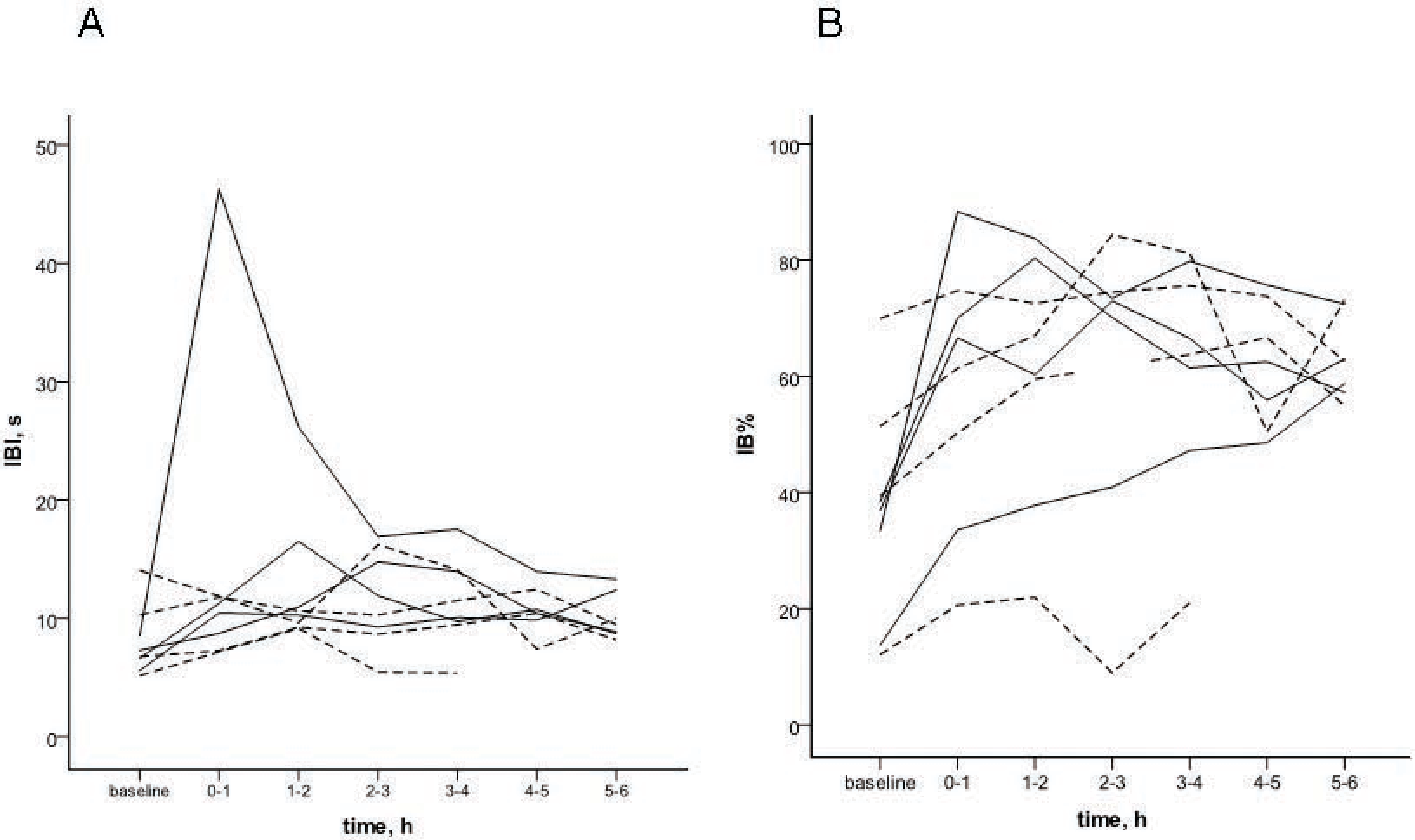
Figure 4. Consort flow chart



A
Burdjalov score, total
Time, h
0-3
3-6
6-9
9-12
12-15
15-18
18-21
21-24
B
Background pattern
Time, h
C
Interburst interval (IBI)
Time, h
D
Interburst % (IB%)
Time h



Elisabeths Bild
15 mm/sec
70 µV/cm
15 Hz
0,160 Hz
aEEG
F3-P3 Vä
[µV]
aEEG
F4-P4 Hö
[µV]
TCD
ABP-HP
Events
02:00:00
02:00:30
02:01:00
02:01:30
02:02:00
02:02:30
02:03:00
02:03:30
inj morphine
F3-P3
F4-P4
ABP-HP
Pleth-Nell
02:57:04 Elisabeths Bild, 15 mm/sec, 70 µV/cm, 15,0 Hz, 0,160 Hz, Notch Off



A
IBI, s
0
10
20
30
40
50
baseline
0-1
1-2
2-3
3-4
4-5
5-6
time, h
B
IB%
0
20
40
60
80
100
baseline
0-1
1-2
2-3
3-4
4-5
5-6
time, h

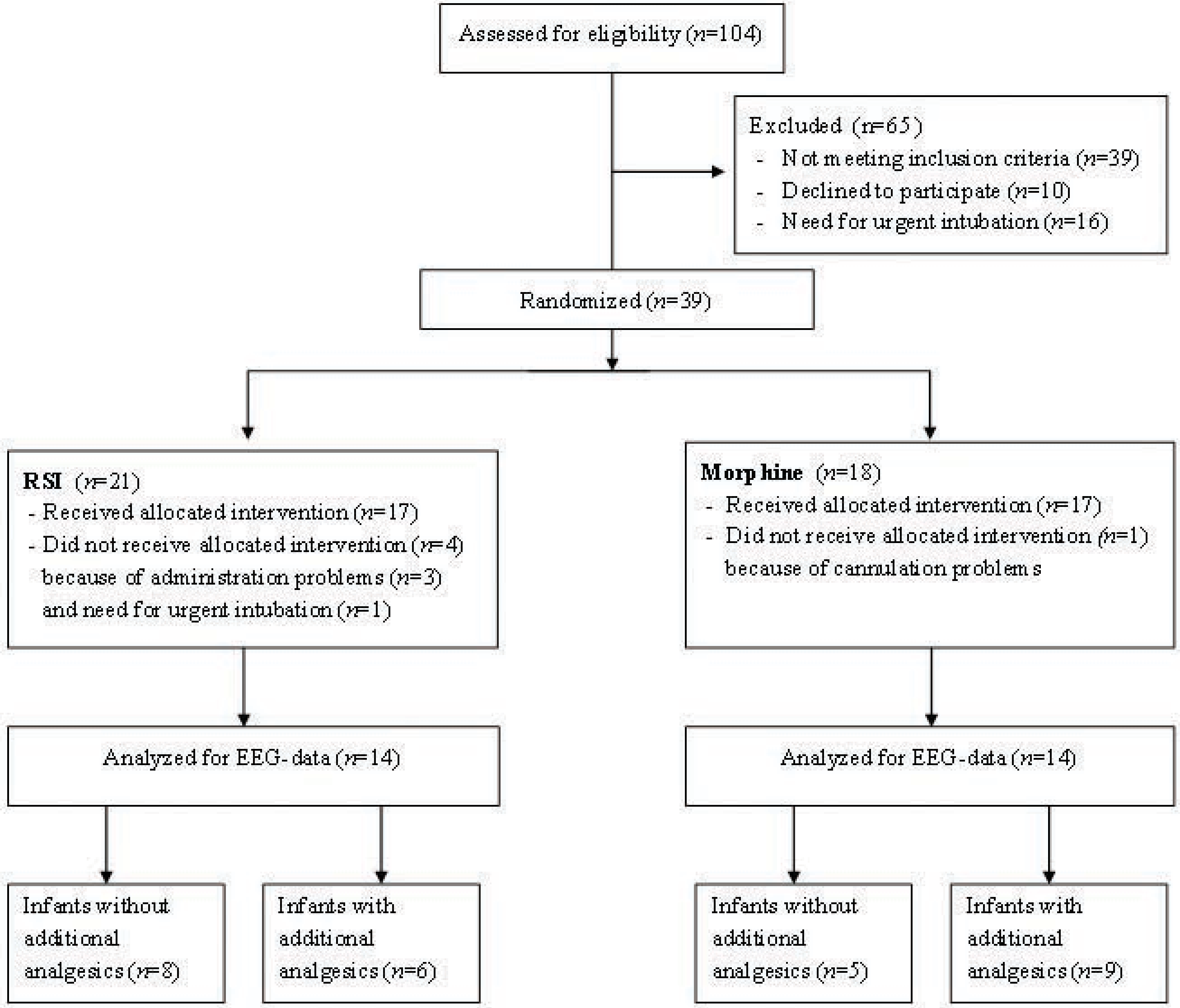

Assessed for eligibility (n=104)
Excluded (n=65)
- Not meeting inclusion criteria (n=39)
- Declined to participate (n=10)
- Need for urgent intubation (n=16)
Randomized (n=39)
RSI (n=21)
- Received allocated intervention (n=17)
- Did not receive allocated intervention (n=4) because of administration problems (n=3) and need for urgent intubation (n=1)
Morphine (n=18)
- Received allocated intervention (n=17)
- Did not receive allocated intervention (n=1) because of cannulation problems
Analyzed for EEG-data (n=14)
Analyzed for EEG-data (n=14)
Infants without additional analgesics (n=8)
Infants with additional analgesics (n=6)
Infants without additional analgesics (n=5)
Infants with additional analgesics (n=9)

Table 1. Mean arterial blood pressure during the 24 h study period in the infants who did not receive additional morphine boluses, mean and IQR values

Time, h	**RSI** (*n*=8)	**Morphine** (*n*=5)	***P***
0-3	39.5 (29.1-50.5)	28.5 (22.8-30.6)	0.045
3-6	37.3 (26.3-46.8)	27.8 (20.4-29.4)	0.062
6-9	39.9 (32.9-49.3)	27.0 (21.2-31.0)	0.045
9-12	36.7 (25.6-47.2)	29.5 (22.6-31.2)	0.088
12-15	38.4 (26.1-48.6)	29.1 (22.6-32.1)	0.088
15-18	42.7 (34.9-48.6)	32.1 (22.5-32.5)	0.028
18-21	37.1 (26.6-48.5)	31.1 (23.0-32.7)	0.123
21-24	37.5 (30.2-50.0)	26.6 (23.0-32.9)	0.028

Table 2. Demographic and Baseline Clinical Characteristics; infants in total randomization groups and infants who received only the premedication.

	RSI (*n* = 14)	**Morphine** (*n* = 14)	**RSI** (*n* = 8)	**Morphine** (*n* =5)
Male/female, *n/n*	9 / 5	7 / 7	6 / 2	2 / 3
Birth weight, g	852 (734-1078)	794 (701-1015)	963 (731-1263)	1005 (734-1280)
Gestational age at birth, weeks	26.4 (25.5-27.8)	25.7 (24.8-27.7)	26.4 (25.7-28,6)	27.7 (25.0-28.4)
Postmenstrual age at intubation, weeks	27.9 (26.8-29.1)	27.7 (25.8-28.3)	28.9 (26.6-29.9)	27.7 (25.9-28.4)
Postnatal age at intubation, h	136 (24.5-384)	162 (26.8-345)	136 (12.8-480)	8 (6-183)
Hemoglobin, g/l	145 (135-158)	142.5 (133-158)	144 (138-157)	145 (132-182)
Intraventricular hemorrhage				
- grade I, *n*	2	3	1	1
- grade II-IV, *n*	1			

All values are in median and IQR. All differences are nonsignificant.