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

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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, as compared with rapid sequence induction/intubation (RSI).

METHODS: Of 34 infants enrolled in a randomized controlled trial (RCT) comparing RSI (including thiopental 2–3 mg/kg and remifentantil 1 mcg/kg) with morphine (0.3 mg/kg) as premedication for intubation, 28 infants ($n = 14 + 14$; median gestational age 26.1 wk 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 <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 (IBI) were significantly increased as compared with those of RSI treatment. 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.

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). Because amplitude-integrated EEG (aEEG) and EEG monitoring are increasingly used in neonatal intensive care units (NICUs) (12), drug effects on neonatal aEEG/EEG should be characterized in relation to gestational age.

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 semiurgent intubations in infants should be performed after premedication (16,17). In newborns, morphine is still frequently used despite its 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) vs. 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 as compared with RSI.

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 as compared with the eight infants receiving 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

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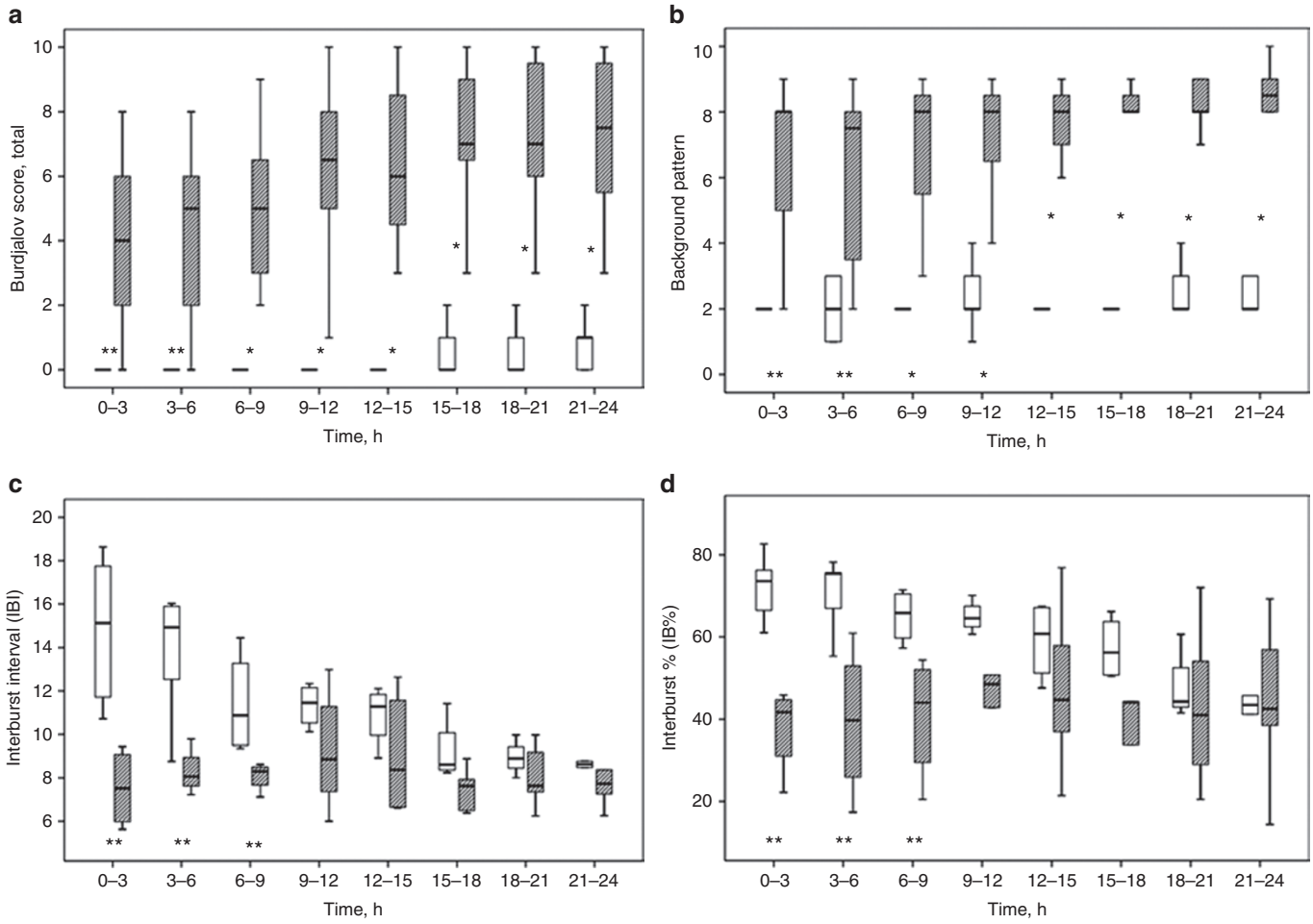

Figure 1. aEEG/EEG data of infants with no additional analgesics after intubation. The (**a**) Burdjalov total scores and (**b**) BG scores differed significantly between the eight RSI (gray bars) and five morphine (white bars) infants during 24 h. During the first three periods both (**c**) interburst intervals and (**d**) interburst percentage differed significantly. *$P < 0.01$; **$P < 0.05$. aEEG/EEG, amplitude-integrated electroencephalogram; BG, background pattern; RSI, rapid sequence induction/intubation.

3-h epochs, and for the other epochs borderline significances between the groups were observed.

Sleep–wake cycling (SWC) was not found during the 24-h study period in any of the morphine infants who only received premedication, while five of the nine 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 0.002–0.014). In the 15 infants who received additional morphine, the SWC scores differed between the two randomization groups only 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 background pattern (BG) scores were significantly lower after morphine premedication as compared with 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 (BS) dominating) and ranging between 7.5 and 8.5 (i.e., mainly continuous background) in the RSI group (*P* values 0.003–0.017), **Figure 1b**. When additional morphine doses were given after intubation, the BG scores of the RSI infants were not significantly different from those of the morphine group. In the total study group, the BG scores were also significantly lower in the morphine group vs. the RSI group for all 3-h epochs during the study period.

Interburst Intervals and Interburst Percentage

In infants with morphine premedication, the interburst intervals (IBIs) and interburst percentage (IB%) differed significantly from those of RSI-treated infants during the first 9 h, **Figure 1c,d**. 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 the IB% was higher in the morphine group as compared with the RSI group during the first 6 h after the intubation.

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

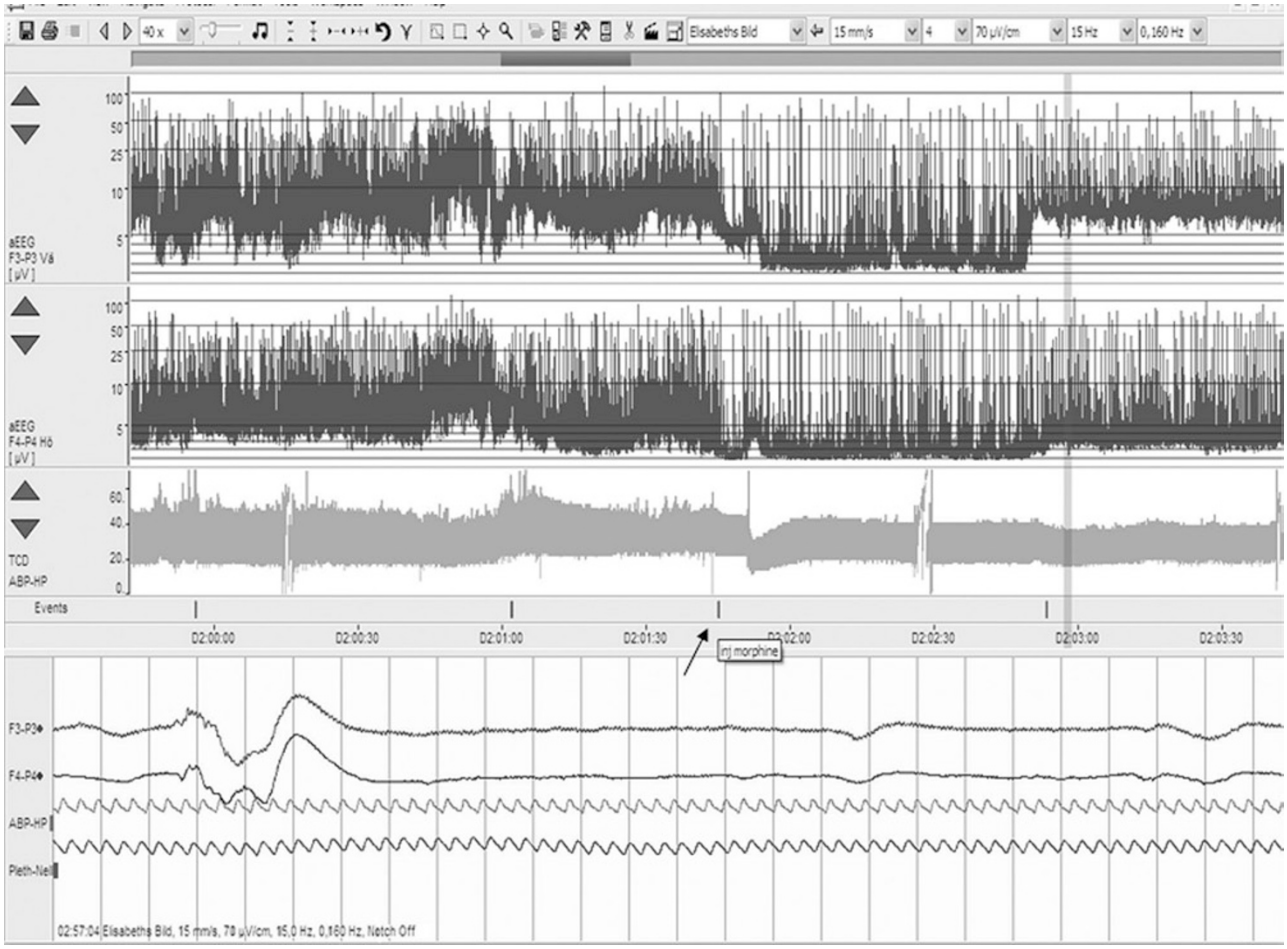

Figure 2. Study monitor with an example of a morphine bolus effect. A recording with time-synchronized two-channel EEG/aEEG, mean arterial blood pressure (MABP), and oxygen saturation (SpO_2, plethysmography), showing a reaction in aEEG and MABP trends from a single bolus dose of morphine (arrow) in a very preterm infant. The three upper traces show 4-h aEEG (left and right electrodes) and MABP trends, and below are shown 25 s of EEG (left and right electrodes), MABP, and SpO_2. The lower border of the F3-P3 aEEG trace is distorted by the addition of an artifact induced by high-frequency ventilation, started at 02.50. aEEG/EEG, amplitude-integrated electroencephalogram.

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 intraventricular hemorrhage (IVH) grade I. Two infants in the morphine group had repeated subclinical seizures, one at 0–9 h and 15–24 h, and one at 3–12 h after the intubation. Neither 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. As compared with 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), whereas IB% continued to be increased 6 h after the bolus (*P* values between 0.012 and 0.028 for all six 1-h epochs, as compared with baseline) (**Figure 3**). There were no differences in this response between the two randomization groups.

Blood Pressure

In the infants who received only 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 with regard to MABP. Univariate ANOVA 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.

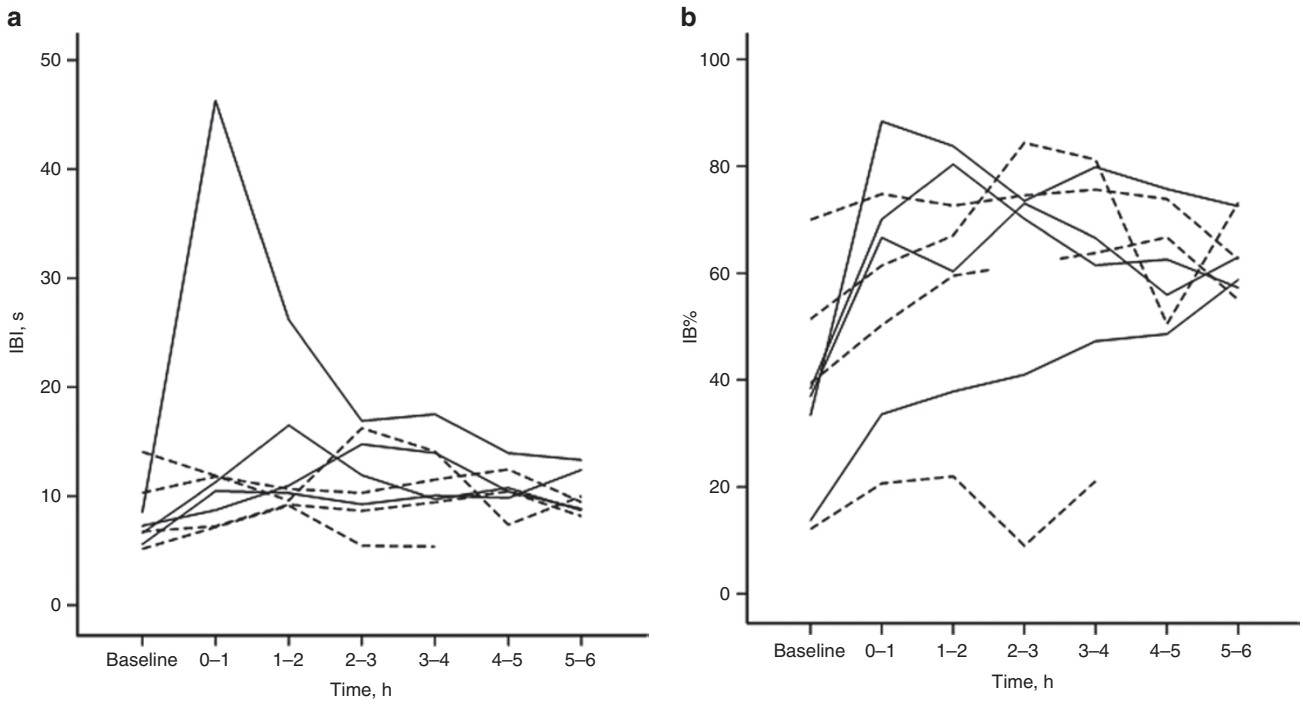

Figure 3. Quantitative data of single doses of morphine. (**a**) IBI and (**b**) interburst percentage were quantified in 1-h epochs up to 6 h after a single bolus dose of morphine, 0.15 mg/kg, administered to four RSI-treated infants (solid lines) and four morphine-treated infants (dotted lines). IB, interburst; IBI, interburst interval; RSI, rapid sequence induction/intubation.

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 value
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

IQR, interquartile range; RSI, rapid sequence induction/intubation.

DISCUSSION

The main finding of 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 SWC. 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 of 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 semiurgent intervention referring to a previous study that showed that a moderately high dose of morphine, 0.2 mg/kg, had no positive effects as compared with 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 a prolonged neurodepressive effect of a single high bolus dose of morphine. However, in a limited number of infants, the EEG remained depressed for more than 6 h 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

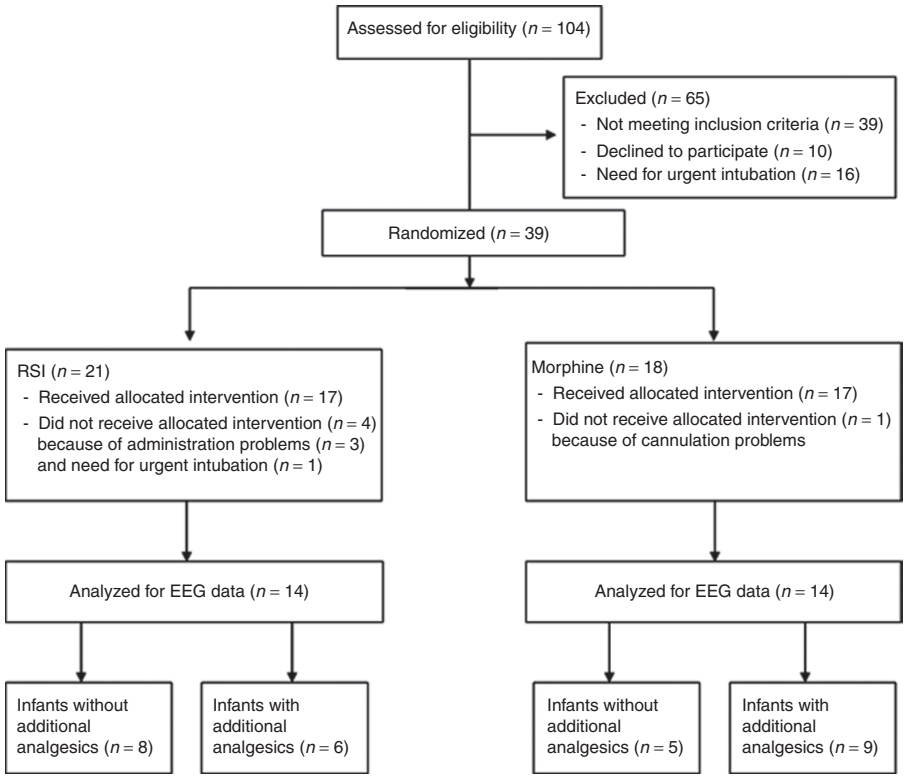

Figure 4. Consort flow chart. EEG, electroencephalogram; RSI, rapid sequence induction/intubation.

Table 2. Demographic and baseline clinical characteristics of 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 (734–1,078)	794 (701–1,015)	963 (731–1,263)	1,005 (734–1,280)
Gestational age at birth, wk	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, wk	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 median and IQR. All differences are nonsignificant.

IQR, interquartile range; RSI, rapid sequence induction/intubation.

and colleagues 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 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 rapid eye movement 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 <3 h 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 from those of thiopental. Currently available information on remifentanil effects in preterm infants is consistent with our data, 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 our 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). Furthermore, 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 vs. 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 the fact 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 γ-aminobutyric acid dependent, and that γ-aminobutyric acid 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 on the cortical activity and potential seizures in infants receiving morphine infusions and other drugs that might have cerebral side effects.

The lack of aEEG/EEG baseline data before the intubation is a limitation in our study. All infants needed semiurgent 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 who 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 BG, and lack of SWC persisting for 24 h. In contrast, RSI premedication with thiopental and remifentanil resulted in shorter EEG depression and less extensive 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.

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 clinicaltrials.gov as no. NCT00216944. Written informed consent was obtained from both parents before enrollment. The study protocol and all the analyses were carried out in a blinded fashion (19).

Patients

Inclusion criteria in the RCT were as follows: need for semiurgent intubation (due to, e.g., respiratory distress syndrome, patent ductus arteriosus, or sepsis), prematurity with gestational age <37 wk and no analgesic or sedative drugs administered during the previous 24 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 who were randomized, 28 infants with a gestational age <32 wk 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**. IVHs were diagnosed in five 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 <1,000 g, 3 mg/kg if ≥1,000 g), suxamethonium (2 mg/kg) and remifentanil (1 μg/kg), or atropine (0.01 mg/kg), and morphine (0.3 mg/kg) as premedication before semiurgent 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 and the Astrid Lindgren and Lund Childrens' Hospitals Pain Assessment Scale for premature infants) 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 1–4 (median 1, no difference between randomization groups) additional doses of morphine, six infants in the RSI group and nine 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, eight in the RSI group and five in the morphine group, received only the allocated premedication, **Figure 4**.

A two-channel 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) continuously after the intubation, starting 20 min after the procedure was completed. Hydrogel electrodes (Ambu Neuroline, Ambu A/S, Ballerup, Denmark) were applied after gentle skin preparation with NUPREP

cream (GRASS Technologies, West Warwick, RI) 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, Sweden, and Nellcor N395 PulseOximeter, Nellcor Puritan Bennett, Pleasanton, CA) from baseline before the premedication, and the data were transferred to the Nervus/Nicolet monitor for concomitant data processing, **Figure 2**. In addition to that, near infrared spectroscopy monitoring was performed during the period of drug administration and intubation and the following 20 min. 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), 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 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 trace discontinued, but not 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 with minimal activity) or inactive (35). The aEEG/EEG background was scored by two assessors together (E.N. and L.H.-W.). Suspected seizures in the aEEG trace were verified (or invalidated) by inspection of the EEG by a clinical neurophysiologist (I.R.).

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

To assess the effect of a single bolus dose of morphine on the EEG, the IBIs and IB% were averaged per hour 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 hour 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. Nonparametric and parametric statistics were applied as appropriate and included Mann–Whitney U test, Wilcoxon signed ranks test, Student's *t*-test, 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 also performed 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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