Peer reviewed article

Pain relief in ventilated preterm infants during endotracheal suctioning: a randomized controlled trial

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Summary

Background: In Switzerland approximately 8% of infants are born prematurely. Some of them undergo mechanical ventilation including endotracheal suctioning (ETS). ETS is one of the most frequently performed interventions and is linked to stress and pain, but its treatment is controversial. In Switzerland there is a lack of standardisation in pain relief for ETS.

Aims: To test the hypothesis that an intermittent dose of morphine reduces pain during ETS and that subsequent multisensorial stimulation (MSS), as a non pharmacological comforting intervention, helps infants to recover from experienced pain.

Method: A randomized placebo controlled trial in two tertiary neonatal intensive care units (NICU) with a sample of 30 mechanically ventilated preterm infants was conducted. Pain was measured by three pain assessment tools (Bernese Pain Scale for Neonates, Premature Infant Pain Profile and Visual Analogue Scale)

Results: Morphine did not lead to any pain relief from ETS as measured by three pain scales. Nor did the comforting intervention of MSS show any effect. Repeated-measure analysis of variance for the within and between groups comparison showed no statistical significance.

Conclusions: The administration of morphine for pain relief in ventilated preterm neonates during ETS remains questionable and the use of MSS as a comforting intervention after painful stimulus cannot be recommended. The validity testing of the instruments for this patient population should undergo a systematic validation trajectory. Future research should focus on options among non pharmacological interventions for relieving pain during ETS.

Key words: preterm infants; pain relief; morphine; multisensorial stimulation

Introduction

In Switzerland approximately 8% of infants are born prematurely and 3% of these require mechanical ventilation with a mean intubation time of 6.75 days [1]. As part of their intensive care these infants undergo endotracheal suctioning (ETS), which is one of the most commonly performed nursing procedures in infants who are being ventilated [2–4]. ETS is associated with stress and pain and its use is therefore a matter of ongoing discussion. A related problem is that there is insufficient evidence to recommend routine use of opioids in ventilated newborns [5]. Although opioids and especially morphine are used in neonates for the treatment of procedural and postoperative pain and pain during mechanical ventilation, concerns exist about potential side effects such as urinary retention, constipation and necrotising enterocolitis [6–8]. Furthermore, preemptive morphine infusions, additional morphine and lower gestational age are associated with hypotension among preterm neonates [9]. These possible side effects might explain the reluctance

Investigator initiated and investigator driven study with no financial support.

to use opioids [10] and their underutilisation in NICUs in particular [11–13].

The results of the NEOPAIN randomised trial of morphine analgesia in ventilated preterm neonates showed that morphine use did not alter the risk of severe intraventricular haemorrhage (IVH) except in infants with a gestational age of 27–29 weeks, periventricular leukomalacia (PVL) or death within 28 days [14, 15]. In a subsequent analysis, the authors concluded that the use of morphine prolonged the duration of mechanical ventilation. Similar results are shown by Simons et al. [16] who describe a decreased incidence of IVH (23% vs 40%, p = 0.04) in the group receiving morphine. However, morphine had no protective effect on poor neurological outcome as defined by severe IVH (grade 3 and 4) or death.

The efficacy of morphine in pain relief is equally questionable. Continuous morphine infusion was found to have no apparent analgesic effect in some studies [16, 17] while Anand et al. [14] found that pain scores were slightly reduced. In contrast, a meta-analysis carried out by Anand and Hall [18] showed significantly lower pain scores in the morphine group. Thus, it has been recommended that opioid analgesia should be limited to the treatment of severe or repetitive pain in preterm neonates or clinical situations in which it provides short-term clinical benefit [14].

Increasingly, non pharmacological pain relieving interventions are discussed [19]. Multisensorial stimulation (MSS) that addresses the neonate at a number of different sensory levels (auditory, orogustatory, tactile) has been described as pain relieving for heel-prick [20]. Facilitated tucking as a further non pharmacological intervention might add to diminishing the pain/stress from ETS [21].

In contrast to the above studies that were testing a continuous administration of morphine, the aim of the present study was to determine the effects of an intermittent dose of morphine on pain resulting from ETS as well as to investigate the effect of MSS after pain exposure. Furthermore, the number of routine procedures infants were exposed to was of additional interest.

Methods

Hypothesis and endpoints

We hypothesized that pain could be reduced by administering an intravenous dose of 0.1 mg/kg of morphine (primary endpoint) and that MSS would help to recover from a painful stimulus particularly in the group receiving a placebo (secondary endpoint).

Design and setting

A randomized controlled trial and a factorial design were used. The sample was recruited from two tertiary level NICU's in Switzerland with 32 (site 1) and 19 (site 2) beds respectively. Thirty preterm infants who required mechanical ventilation and were ventilated for over 13 hours were included. The sample was divided into four groups (morphine vs placebo and multisensorial comforting techniques vs standard comforting techniques) covering all neonates born from 1st May 2004 to 30th April 2006 and admitted to the NICU for mechanical ventilation.

Sample, inclusion and exclusion criteria

All preterm neonates 24 to 37 weeks postmenstrual age based on early ultrasound who were intubated and mechanically ventilated were eligible for inclusion. The data analysis for the effect of morphine and the effect of MSS included the first five days of mechanical ventilation. Data on morbidity covered the entire hospitalisation period until discharge or transmission to another hospital. Eligibility for study inclusion was validated by neonatologists and a clinical nurse specialist in the first 24 hours after birth. The following criteria for exclusion were set: Preterm infants a) with diagnosed IVH grade III and IV b) suffering from any condition involving partial or total loss of sensitivity c) who had been given morphine intravenously up to 10 hours before the study started d) with an APGAR score <3 after 5 minutes or with a cord blood pH of <7.00 e) whose mothers were drug addicts f) who were ventilated after surgery. The original sample size (n = 100; n1 = n2 = 50 subjects in each group) was based on the ability to detect a difference of ½ σ in the mean pain score in the two groups measured primarily by the Bernese Pain Scale for Neonates (BPSN). The power calculation was based on a two sample t-test, one-sided test at a significance level of alpha = 0.05 and a power level of 80% using the NCSS trial and PASS 2000 program.

Study procedures

Inclusion and investigation procedure

In case an infant was eligible for inclusion, final informed consent from the parents was obtained. Whenever possible, preterm infants were included in the study from the first day of intubation. In order to identify IVH, a cranial ultrasound was carried out by a physician in the first 24 hours of life.

Randomization procedure

As shown in figure 1, preterm infants were selected at random for the type of treatment they were to receive. The selection was based on a computer list regarding medication (morphine or a placebo) as well as comforting technique after suctioning (MSS or standard technique). Allocation concealment was made by the study investigator for both interventions and for each infant, and the allocation was included in the same sealed opaque envelope. The envelopes were sequentially numbered. The medication itself was pre-prepared, labelled and numbered according to the computer generated list in the correct dose by the hospital pharmacy in order that nurses administrating the medication could just refer to the number on the medication being in line with the study subject number of the envelope. The two medications were of identical appearance. An attending neonatologist in the participating NICUs identified potential neonatal subjects and communicated this information to a member of the research team. A member of the research team approached the parents of potentially eligible neonates and explained the study to the parents. After re-

ceiving informed consent the primary investigator or the study nurse opened the envelope and assigned the child according to its number to one of the treatment groups. In the case of assignment to the morphine groups, a dose of 0.1 mg/kg was set for this study. Neither the prescribing neonatologists nor the nurse on shift duty administrating the medication before ETS and performing ETS itself nor the assessing shift nurse knew which type of medication was given. Each time a child needed to be suctioned the nurse on duty for this child administrated the allocated medication and a nurse colleague assessed the pain during the 4 time intervals. The interval between treatments depended on the need for suctioning in the individual infant and was decided by the nurse in charge. In view of the long half-life of morphine in preterm infants, an interval of six hours was set for repeating medication during ETS. If suctioning the infant became necessary sooner, the medication was either modified accordingly (0.05 mg/kg) or not given at all. Additional open-label morphine was allowed if infants were considered to be in pain, as verified by a pain score.

Intervention procedure

Routine ETS was carried out by qualified and trained nurses, who administered the iv medication five minutes before the ETS. After suctioning, the infant was comforted either by randomized MSS or by using a standard method (holding the child in the incubator) by the same nurse for two to three minutes. Through MSS, the preterm is calmed after a painful procedure by massaging the back and face. A few drops of a vanillin-oil are spread onto the nurse's hand used for massaging (orogustatory level) and the child is also spoken to gently (auditory level). Furthermore, the infant is provided with a cotton wool stick sprinkled with sucrose so that he/she can suck on it (olfactory level). Using all three pain assessment tools (see section 2.4.1), a second qualified and trained nurse on duty, who did not observe the comforting intervention but was called for the assessment immediately after the comforting intervention was completed, performed the scoring.

Data collection

Background demographic data were collected from nursing and medical charts. A standardized document listing 27 routine procedures was used to record the number of painful procedures throughout the first 14 days, highlighting the most common painful procedures neonates are exposed to (22, 10 and 2). The list was developed based both on a review of the literature and expert opinion, and included standardized routine procedures (e.g. capillary heel lance, endotracheal suctioning, venepuncture, diaper change, intubation etc.). The list was used to record the daily procedures a child included in the study was exposed to during the first 14 days of life.

Pain measurements

Since there is no gold standard for measurements of pain in ventilated preterm infants, the present study simultaneously used the "Bernese Pain Scale for Neonates" (BPSN) [23], the "Premature Infant Pain Profile (PIPP) [24] and the "Visual Analogue Scale" (VAS) [25]. BPSN and PIPP are both multidimensional tools used to objectify acute pain that has demonstrated satisfying psychometric properties among preterm and term neonates in validation studies. The BPSN measures nine indicators, two of which are observed on the monitor (heart rate and oxygen saturation) and seven clinically (grimacing, body movements, crying, skin colour, sleeping patterns, respiration, consolation). Validation of the BPSN showed construct validity with a differentiation between painful and non-painful procedures ($F = 41.27$, $p < 0.0001$), inter-rater reliability coefficients of $r = 0.86–0.97$ and intrarater reliability of ($r = 0.98–0.99$). In the BPSN-scaling, scores of <11 are considered to be non-painful. The PIPP measures gestational age, behavioural state, heart rate, oxygen saturation, and three facial reactions (brow bulge, eye squeeze, and nasolabial furrow). Validation of the PIPP score showed construct validity with an ability to differentiate painful from non-painful procedures or baseline events (p 0.0001), inter-rater reliability coefficients of 0.93 to 0.96, and intra-rater reliability coefficients for individual events of 0.94 to 0.98. The cut-off score for a painful state of the PIPP was set at 12 points. The VAS has been recommended as a tool for assessing pain in clinical studies whose cut-off of a painful state has been set at 4 points. In the present study, it was used to compare objective and subjective assessment of pain by the rating nurse. Pain was assessed at four intervals: (T0) at the baseline before administration of study medication; (T1) after administration of an analgesic, five minutes before ETS; (T2) during ETS; (T3) two-three minutes after comforting interventions (MSS or holding the child). Measurements were made up to the fifth day of intubation.

Statistics

While data were analysed descriptively and exploratively using means and standard deviations, hypotheses were examined using variance analysis (univariate analysis and the general linear model). The within-subjects factors were the pain scores of the BPSN, PIPP, VAS at T0, T1, T2, T3; the between-subjects factor was the treatment group (placebo versus morphine). Mauchly's test of sphericity was verified before interpretation of results. Nominal variables were compared with Fischer's exact tests (for contingency tables with small cell frequency). In case data were not distributed normally, non-parametric procedures were used. Comparing MSS and standard comforting, we expected that infants in the placebo group would be comforted more quickly through MSS. Since this variable was measured at T4, a point in time at which the design was a factorial one, we fit a rank-transformed ANOVA including the variables morphine, MSS and their interaction. No power analysis was done in this respect. All data were compiled into an SPSS file (Version 14). The assumptions for parametric tests were verified by Q-Q-Plots.

Ethical considerations

In the two participating hospitals, the clinical routine of analgesia for ETS intervention is characterised by heterogeneity. While at one centre, no pre-emptive analgesia is given at all, the other site administers Pethidine (Meperidine). The latter represents a practice that is not recommended [26] due to its potential to cause central nervous system irritability and convulsion due to accumu-

lation of the drug and its metabolite [27, 28]. The "no treatment" as part of standard care at one site, the use of a potentially harmful agent at the other as well as the lack of evidence for the pain relieving effect of morphine led the author group to agree that the trial with a placebo group was ethically acceptable according to international consensus [29].

In order to ensure that infants in the placebo group received some basic level of pain relief, each preterm infant enrolled in the study was given 0.1 ml/kg of 30% glucose orally in addition to the morphine or placebo. Glucose has provided sufficient evidence for pain relief [30] and is not a strong analgesic but simply reduces sensitivity to pain.

The study was approved by all local ethics committees (two in the Canton of Bern; main ethical board and sub-commission for paediatrics and two in the Canton Zürich; main ethical board and sub-commission for paediatrics) according to national and local regulations. Written informed parental consent was obtained according to local rules.

Problems of patient recruitment

As encountered by Ballard et al. [31] and following the ethical principal that parents should understand intention and aim of the study, achieving such understanding required several conversations with parents before they gave their consent. Since migrants make up 45% of the hospital population – some of them with refugee status and no command of the local language – adequate information provision was not always possible. Refusal rate was 22.2% with an additional 12.2% of parents of the preterm infants born in the respective period not approached at all because of insufficient communication skills due to migrant status or heavy psychosocial burden.

Results

Background demographics and clinical characteristics of the study sample

During the study period, 120 infants needed mechanical ventilation and 30 infants were enrolled in the study (fig. 1). None of the infants dropped out of the study; all remained in their assigned study group. No differences in perinatal characteristics between the morphine and placebo

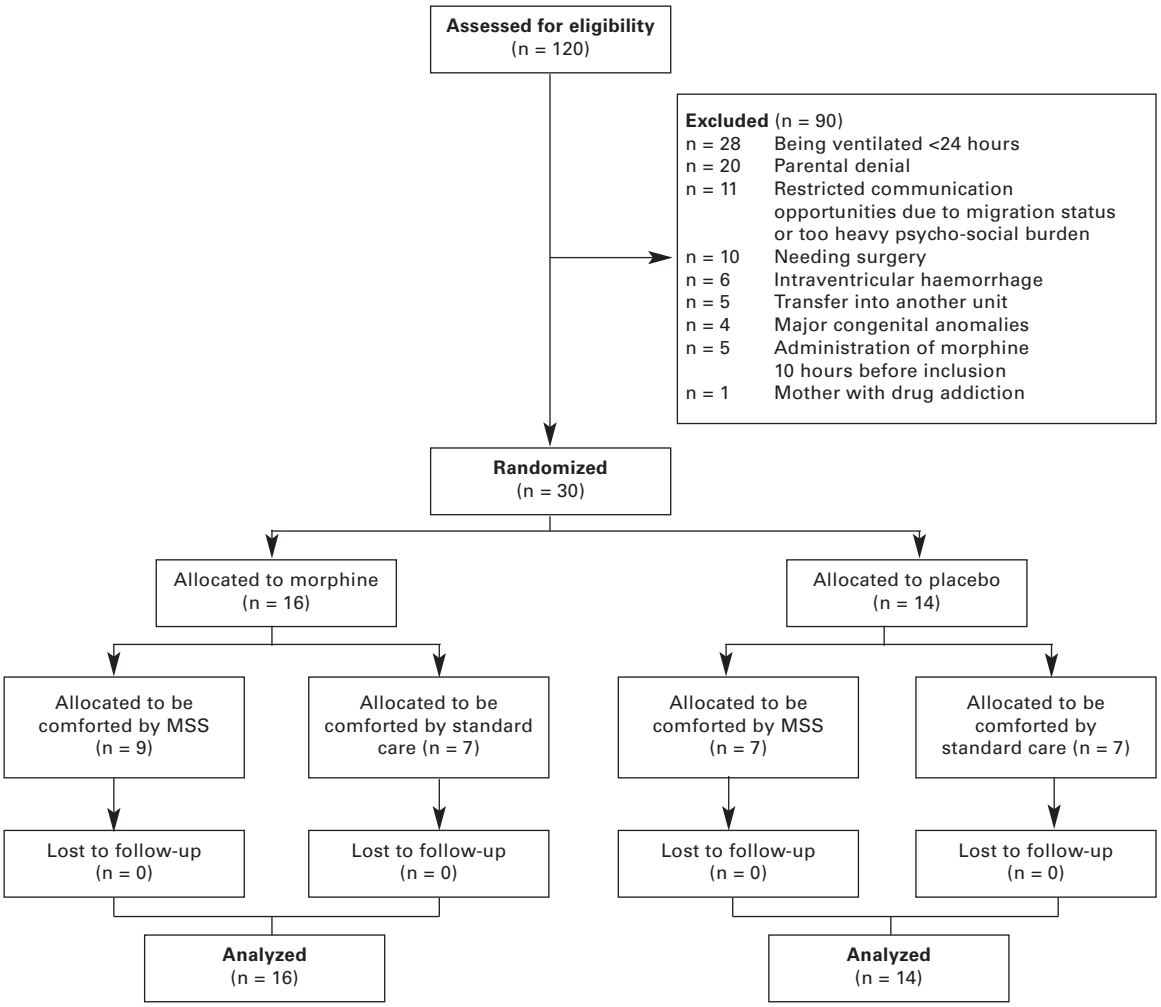


Figure 1
Diagram of randomisation and investigation.

groups were observed (F 1; table 2). Mean ventilation time duration and thus mean time for intermittent administration of morphine, was 86.0 hours for the morphine group and 65.2 hours for the placebo group (F 0.459; p = 0.53). Open-label morphine was administered to six infants in the morphine group and six infants in the placebo group with a mean dose of 0.18 mg/kg (SD 0.44) in the placebo group and 0.05 mg/kg (SD 0.09) in the morphine group (F1.383; p = 0.25).

The number of procedures carried out during ventilation was 3'082 for the entire sample. The mean number of procedures for the placebo group was 89.57 procedures (± 109.45) compared with 114.25 (± 111.77) in the morphine group (F0.371 ; p = 0.54). During the first 14 days of life 10'638 procedures occurred in all 30 preterm infants, showing no difference between the study groups (F0.215; p = 0.64). According to this result, each preterm infant was on average exposed to 354.6 procedures in the first two weeks of life or 25.3 procedures per day.

Effect of morphine

Mean pain scores for both groups are shown in table 3. Overall, pain scores did not differ significantly between the two groups. Due to the potential lack of behavioural reactions in preterm infants, one calculation included only the physiological indicators measured by the BPSN (mean of the increase in heart rate and mean of the decrease in oxygen saturation) to verify whether physiological changes could indicate a reaction to pain independently from behavioural indicators. Table 3a shows no statistically significant differences in the mean pain score as measured by heart rate and oxygen saturation between the two groups. Table 4 shows the results of the repeated-measure analysis of variance for the within and between group comparisons of pain scores using BPSN, PIPP and VAS. Mean pain scores induced by ETS (pain at T0 – T3) show a statistical difference for the total scores of BPSN (F20.358 p 0.000), for the PIPP (F11.519 p 0.000) and for the VAS (F17.74 p 0.000) over time (see also fig. 2). The within group analysis of interaction between time factor and treatment group detected no statistical significance, neither for BPSN (F1.060 p 0.359), PIPP (F0.092 p 0.932) nor for VAS (F1.099 p 0.347). Furthermore, the analysis for the BPSN with physiological parameters showed no statistical difference, neither for the mean pain

Table 1
Background demographic and clinical characteristics.

	Morphine (n = 16)		Placebo (n = 14)	
	N	**%**	**N**	**%**
Gender				
Male	10	37.5%	11	78.6%
Female	6	62.5%	3	21.4%
Total pro study group	**16**	**100%**	**14**	**100%**
Gestation from 24–28 weeks	9	56.3%	8	57.1%
Gestation from 28–32 weeks	5	31.3%	3	21.4%
Gestation from 32–37 weeks	2	12.5%	3	21.4%
Patients receiving additional open label morphine	6	37.6%	6	42.7%
Patients receiving multisensorial stimulation	9	56.2%	7	50.0%
Patients receiving standard comfort technique	7	43.7%	7	50.0%

All values expressed as amounts (%)

Table 2
Outcome variables.

	Morphine (n = 16)		Placebo (n = 14)		Level of significance (p value)	95% CI
Outcome variables	**Mean**	**SD**	**Mean**	**SD**		
Gestational age	28.17	3.00	28.08	3.93	$F_{0.006}$ p 0.940	26.83–29.42
Birth weight (g)	1113.44	562.46	1110.21	703.50	$F_{0.000}$ p 0.989	881.29–1342.35
Apgar 1 minute	4.38	1.996	4.5	2.53	$F_{0.023}$ p 0.881	3.59–5.28
Apgar 5 minute	6.63	2.15	6.7	2.15	$F_{0.053}$ p 0.820	5.99–7.42
Ventilation time in hours	86.0	79.81	65.29	87.56	$F_{0.459}$ p 0.503	44.343–106.942
Amount of suctioning procedures during study time	13.73	8.98	11.29	12.23	$F_{0.381}$ p 0.542	8.43–16.58
Amount of procedures during intubation time	114.25	111.77	89.57	109.45	$F_{0.371}$ p 0.547	60.41–143.40
Amount of procedures during the first 14 days of life	356.47	127.42	377.93	121.28	$F_{0.251}$ p 0.646	319.73–414.66
Weight at discharge (g)	2207.33	835.25	2306.54	858.35	$F_{0.096}$ p 0.759	1983–2456
Head circumference at discharge (cm)	33.93	7.02	33.30	3.01	$F_{0.094}$ p 0.762	32.14–34.26

All values expressed as means (standard deviation)

Table 3

Pain scores induced by endotracheal suctioning performed before any intervention (T0), after i.v. administration of study medication (T1), during endotracheal suctioning (T2) and after comforting technique (T3).

	Morphine (n = 16)		Placebo (n = 14)		Level of significance (p value)
	Mean	SD	Mean	SD	
Bernese Pain Scale for Neonates (BPSN)					
T0	3.54	2.69	4.45	2.22	$F_{0.012}$ p 0.914
T1	3.64	2.80	3.05	1.57	$F_{0.484}$ p 0.492
T2	6.67	2.54	7.62	2.94	$F_{0.907}$ p 0.349
T3	3.23	2.35	4.35	4.28	$F_{0.821}$ p 0.373
Premature Infants Pain Profile (PIPP)					
T0	5.49	1.82	5.01	1.53	$F_{0.581}$ p 0.452
T1	5.43	0.98	4.84	1.28	$F_{2.047}$ p 0.164
T2	6.84	1.54	6.61	2.08	$F_{0.116}$ p 0.736
T3	4.86	1.85	4.51	2.48	$F_{0.188}$ p 0.668
Visual Analogue Scale (VAS)					
T0	16.76	16.94	14.96	11.93	$F_{0.110}$ p 0.742
T1	15.42	11.84	11.92	8.30	$F_{0.856}$ p 0.363
T2	28.97	15.03	33.03	16.35	$F_{0.502}$ p 0.484
T3	9.54	6.44	14.84	19.97	$F_{1.010}$ p 0.323

Table 3a

Mean of total physiological pain scores only of the BPSN.

	Morphine (n = 16)		Placebo (n = 14)		Level of significance (p value)
	Mean	SD	Mean	SD	
Bernese Pain Scale for Neonates (BPSN)					
T0	0.20	0.36	0.20	0.49	$F_{0.000}$ p 0.988
T1	0.18	0.31	0.19	0.31	$F_{0.010}$ p 0.920
T2	0.90	0.80	1.26	0.71	$F_{1.485}$ p 0.234
T3	0.52	0.73	0.42	0.58	$F_{0.148}$ p 0.704

Table 4

Results of the repeated-measures analysis of variance for within- and between-groups factors comparing scores during ETS (T0–T3).

Source	Sum of squares	DF	F	P
BPSN – Within group				
Time (T0, T1, T2,T3)	293.4	2	20.35	0.00
Interaction of time and treatment group	15.2	2	1.06	0.36
Error-time	403.5	62		
BPSN – Between group	3.6	1	0.22	0.64
Error	445.7	28		
PIPP – Within group				
Time (T0, T1, T2,T3)	70.1	2	11.51	0.00
Interaction of time and treatment group	0.6	2	0.09	0.93
Error-time	170.5	64		
PIPP – Between group	4.9	1	0.82	0.37
Error	169.8	28		
VAS – Within group				
Time (T0, T1, T2,T3)	6746.1	2	17.74	0.00
Interaction of time and treatment group	418	2	1.09	0.35
Error-time	10647.7	66		
VAS – Between group	**30.6**	**1**	**0.077**	**0.78**
Error	11191.6	28		

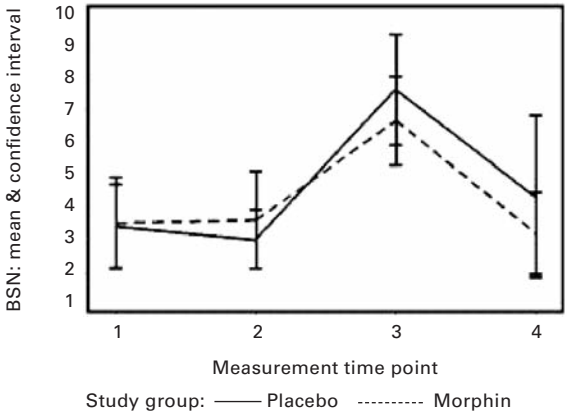
Table 4a

Results of the repeated-measures analysis of variance for within- and between-groups factors comparing BPSN physiological scores only during ETS (T0–T3).

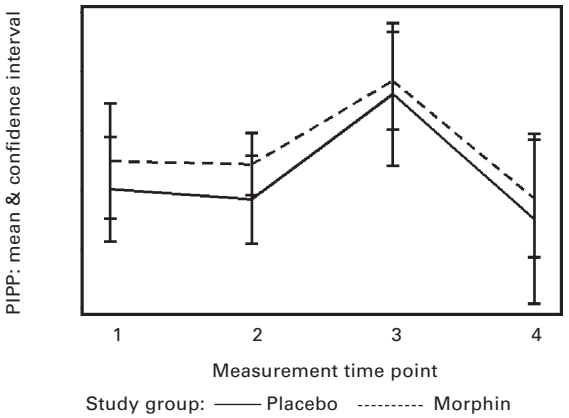
Source	Sum of squares	DF	F	P
BPSN within-group				
Time (T0, T1, T2,T3)	0.8	3	0.847	0.46
Interaction of time and treatment group	0.0	1	0.002	0.97
Error-time	9.5	25		
BPSN – Between group	0.1	1	0.345	0.56

Figure 2

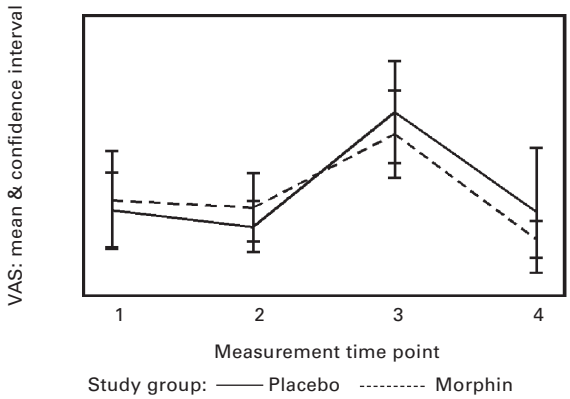
Overall mean measurement and confidence intervals over time period with BPSN, PIPP, VAS.



BSN-Morphin	Mean	95% – CI
Time point 1	3.54	2.14 – 4.94
Time point 2	3.64	2.14 – 5.12
Time point 3	6.67	5.31 – 8.01
Time point 4	3.23	1.97 – 4.48
BSN-Placebo	**Mean**	**95% – CI**
Time point 1	4.45	2.15 – 4.73
Time point 2	3.05	2.13 – 3.95
Time point 3	7.62	5.91 – 9.31
Time point 4	4.35	1.87 – 6.82



PIPP-Morphin	Mean	95% – CI
Time point 1	5.49	4.51 – 6.45
Time point 2	5.43	4.91 – 5.95
Time point 3	6.84	6.01 – 7.66
Time point 4	4.86	3.86 – 5.84
PIPP-Placebo	**Mean**	**95% – CI**
Time point 1	5.01	4.12 - 5.89
Time point 2	4.84	4.09 – 5.58
Time point 3	6.61	5.41 – 7.81
Time point 4	4.51	3.07 – 5.94



VAS-Morphin	Mean	95% – CI
Time point 1	16.76	7.73 – 25.79
Time point 2	15.42	9.11 – 21.73
Time point 3	28.97	20.95 – 36.98
Time point 4	9.54	6.11 – 12.98
VAS-Placebo	**Mean**	**95% – CI**
Time point 1	14.96	8.07 – 21.85
Time point 2	11.92	7.12 – 16.71
Time point 3	33.03	23.58 – 42.47
Time point 4	14.84	3.31 – 26.37

scores over time (F0.847 p 0.457) nor for the interaction of time and treatment group (F0.002 p 0.969) (see table 4a).

Effect of multisensorial stimulation

No statistical effect could be detected when comparing MSS and standard comforting interventions as measured by all assessment tools (table 5). Neither did the effect differ in the infants assigned to the morphine group.

Incidence of morbidity and mortality

Table 6 lists the incidence of morbidity and mortality for the two groups. With the exception of the "inhibition of respiratory drive", statistical testing was not applicable. For the ventilation period, there is a trend towards increased morbidity in the placebo group. For the period from extubation until discharge, there is a trend towards higher urinary retention, a higher constipation rate and higher gastric retention in the morphine group. Overall, five infants died during the first 30 days of life (three in the placebo group and two in the morphine group) and one child was diagnosed with an IVH grade 3.

Table 5

Comparison of the effect of comfort techniques and morphine administration at time point 4.

Pain Score	Medication	Estimate	Standard error	T-value	P-value
BPSN	Intercept	14.57142857	3.36201683	4.33	0.0002
	Morphin	–3.00000000	4.75460980	–0.63	0.5336
	MSS	3.07142857	4.75460980	0.65	0.5239
	Morphin*MSS	2.96825397	6.53458613	0.45	0.6534
PIPP	Intercept	14.00000000	3.31120336	4.23	0.0003
	Morphin	–1.85714286	4.68274870	–0.40	0.6949
	MSS	1.07142857	4.68274870	0.23	0.8208
	Morphin*MSS	6.39682540	6.43582250	0.99	0.3294
VAS	Intercept	15.14285714	3.50820100	4.32	0.0002
	Morphin	–0.07142857	4.96134544	–0.01	0.9886
	MSS	0.35714286	4.96134544	0.07	0.9432
	Morphin*MSS	0.68253968	6.81871709	0.10	0.9210

Table 6

Morbidity and mortality.

	Morphine (n = 16)		Placebo (n = 14)		Level of significance (p value)
	N	%	N	%	
Morbidity during intubation time					
Inhibition of respiratory drive	4	25	1	7.1	N.A.
Urinary retention	1	6.2	2	14.2	N.A.
Constipation (no bowel function for > 48 hours)	4	25	4	57.1	N.A.
Arterial hypotension	6	37.5	6	42.8	N.A.
Morbidity till discharge or till transfer into another hospital					
Inhibition of respiratory drive	11	68.7	11	78.5	0.68 (Fisher Exact Test)
Urinary retention	2	12.5	0	0.0	N.A.
Arterial hypotension	2	12.5	3	21.4	N.A.
Constipation (no bowel function for 48 hours)	6	37.5	1	7.1	N.A.
Gastric retention	7	43.7	4	28.5	N.A.
Chronic lung disease	3	18.7	2	14.2	N.A.
Necrotising enterocolitis	1	6.25	1	7.1	N.A.
Regurgitation	4	25.0	4	28.5	N.A.
Sepsis	2	12.5	1	7.1	N.A.
Intraventricular haemorrhage Grade 3 and 4	1	6.25	0	0.0	N.A.
Respiratory Distress Syndrom (RDS)	3	18.7	2	14.2	N.A.
Persistent Ductus Arteriousus (PDA)	6	37.5	5	35.7	N.A.
Pneumonia	1	6.25	4	28.5	N.A.
Death during the first 30 days of life	2	12.5	3	21.4	N.A.

All values expressed as numbers and amounts (%)
N.A.: Statistical testing not applicable

Discussion

As measured with three pain scales, morphine did not reveal any analgesic effect for pain induced by ETS among ventilated preterm neonates, and in this, the findings confirm results from similar studies [14, 16, 17, 32]. Unexpectedly, for the placebo group the comforting intervention of MSS did not show a difference in the mean pain score compared to the standard comforting intervention. In contrast to Anand et al. [14], no statistical difference in the ventilation time between the two groups was shown. However, the morphine group showed a tendency towards a difference, with a higher mean intubation time of almost 20 hours. According to the clinical judgement of nurses and physicians, open-label morphine was administered if the infant was assessed as being in pain (either by objective measurements or by clinical observations of restlessness). The use of open-label morphine was higher in the placebo group (mean dose 0.18 mg/kg, mean dose 0.05 mg/kg respectively). The open-label morphine was given only in situations where the child was believed to be in pain, independently of the endotracheal suctioning procedure

and the application strictly adhered to international guidelines [26], allowing the administration of 0.05 to 0.1 mg/kg of morphine in an interval of 4–6 hours. Due to the long half-life of the substance in the immature organic system of preterm infants, we can not exclude that the higher administration of morphine in the placebo group could have affected the following measurements during the intervention under investigation.

The main results need to be considered with the major methodological caveat of this study being underpowered. A post hoc power analysis revealed that the power of the study is 0.152, this in accordance with the mean and SD of the BPSN during ETS, with alpha set at 0.05 and a sample size of n = 30, based on a one-way ANOVA. Although the study period lasted almost 2 years, only 30 infants were included in the study. Due to practical and financial constraints, an extension of the study period was not possible. Nevertheless, we believe that the study provides relevant findings that deserve dissemination and further discussion.

Possible explanations for the inefficacy of morphine

The lack of analgesic effect deserves a critical reconsideration of aspects of hormonal responses and the potentially affected behavioural responses in neonates after birth. Given that children were enrolled within 24 hours after birth, the low pain scores may be due to the release of endorphines during the birth process [16] providing a protective effect against noxious stimuli. However, reports of Beta-endorphin changes over time indicate a decrease two hours after the stress of birth or intubation [33, 34]. For the sampled infants included 6–10 hours after intubation, the explanation of a protective endorphin level does not seem convincing. The immaturity of opioid receptors [35–37] among preterm neonates, the decreased production of morphine-6-glucuronide and increased production of morphine-3-glucuronide [38] might provide alternative explanations for the lack of effectiveness of morphine.

A further aspect influencing pain assessment has been postulated by Als [39–41], suggesting that preterm infants in NICUs become disorganized under the extreme stress of preterm birth and the subsequent intensive care treatment. Consequently, due to exhaustion resulting from extreme stress they are not able to respond coherently to noxious stimuli.

Furthermore, pain experienced during ETS might not be severe enough to generally warrant the use of morphine [14]. A survey of 400 health care providers [42] on the presumed intensity of ETS suggests ETS as being one of the most painful procedures of routine care in an NICU – a result that has been confirmed in studies with adults, where the suctioning procedure is associated with pain and anxiety [43]. It is plausible to assume no difference in ventilated preterm neonates. Therefore, the issue of the intensity of pain experienced during suctioning in preterm infants remains inconclusive and needs further investigation.

The lack of pain responses in ventilated preterm infants needs critical reconsideration related to the psychometric properties of the instruments. Lacking a gold standard, measuring the effect of morphine on pain in preterm infants remains difficult. As stated by Bellù et al., [4] a major problem in terms of the primary outcomes of pain relief consists in the different approaches in measuring pain in the different studies analyzed. So far, the validity of BPSN and PIPP relies on preterm neonates not exclusively requiring mechanical ventilation. The BPSN has been validated by good concurrent validity with the PIPP [23], which itself has been used recently in several studies regarding the efficacy of morphine, in addition to having been referred to as a reliable tool for this patient population. The research team of this study considered the BPSN a valid tool for this study. Yet, the mean difference of the BPSN was minus 0.95 (7.62 points vs. 6.67) for the morphine group during ETS (T2) – a result with no statistical significance. The PIPP showed an even higher mean pain score for the measurement during ETS in the morphine group vis à vis the placebo group (6.61 vs. 6.84). Nurses concerned with applying the measurement tools reported considerable difficulties in assessing pain with the PIPP score, since it focuses mainly on the infant's facial expressions. Measuring the latter was very often affected by the tapes fixing the tube as well as by the general immaturity of the very low birth weight children that in turn resulted in less facial action. We thus suggest further validity testing of the BPSN and PIPP if used in this particularly vulnerable patient population.

Lack of efficacy of multisensorial stimulation

In the present study, MSS did not show any pain relieving effect. While acknowledging that the size of the subgroups used for comparing MSS and standard comforting intervention effects puts limits to the generalisation of these findings, none of the instruments showed a significant difference between the groups for this intervention. This results contrasts with the findings of Bellieni et al. [20], whose study showed positive results in a sample of 17 non-ventilated preterm neonates with <35 weeks gestation. It should be noted, however, that we found even higher mean pain scores in preterm infants comforted by MSS than comforted by standard care even in the placebo group, indicating a possible over stimulation of the infant by this comforting techniques.

Number of procedures

During the first 14 days of life 10,638 procedures occurred for all 30 preterm infants, showing no difference between the study groups (F0.215

p 0.646). Thus, each preterm infant was on average exposed to 354.6 procedures in the first two weeks of life or 25.3 procedures per day – a higher exposure to painful procedures than previously reported [2, 3, 10, 44, 45]. This difference in pain exposure might be due to discrepancies in the listing of routine procedures and the inconsistent consideration of failed procedures between studies.

Since the sample size for each event was too small, no substantive conclusion can be drawn regarding the incidence of morbidity and mortality in either of the groups.

Acknowledging that the study was underpowered, we believe that the study nevertheless identifies the questionable psychometric properties of the instruments and the reasons for a lack of pain response as important issues to be critically explored for further investigation of pain management in ventilated preterm infants.

Conclusions

The use of morphine for pain relief during ETS and the use of MSS as a comforting method for very low birth weight children (<1500 g) who are being mechanically ventilated should be critically discussed. Future research should focus on options among non-pharmacological interventions for relieving pain during ETS. Measuring the effect of morphine on the pain experienced by preterm neonates remains a challenge.

This was an investigator initiated and driven study, run with limited funding. The successful completion of the trial was dependent on a dedicated study team willing to take on extra responsibility and work-load in supervising and assuring the rigorous safety-requirements involved. Since resources to finance costs of the study were very limited, our studies had to operate within the existing framework of local neonatal unit and staff personnel.

Financial support is acknowledged from the Executive Directory of Nursing at the University Hospital in Bern, the "Reach Out" project of the "Eleonoren Foundation" of the Children's University Hospital in Zürich and from the "Ettore and Valeria Rossi Foundation" in Berne (Switzerland).

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