

Assessment of Continuous Pain in Newborns admitted to NICUs in 18 European Countries

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.....on behalf of the EUROPAIN survey working group of the NeoOpioid Consortium.

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ABSTRACT

Aim: Continuous pain occurs routinely, even after invasive procedures, or inflammation and surgery, but clinical practices associated with assessments of continuous pain remain unknown.

Methods: A prospective cohort study in 243 Neonatal Intensive Care Units (NICUs) from 18 European countries recorded frequency of pain assessments, use of mechanical ventilation, sedation, analgesia, or neuromuscular blockade for each neonate upto 28 days after NICU admission.

Results: Only 2113/6648 (31·8%) of neonates received assessments of continuous pain, occurring variably among tracheal ventilation (TrV, 46·0%), noninvasive ventilation (NiV, 35·0%), and no ventilation (NoV, 20·1%) groups ($p<0\cdot001$). Daily assessments for continuous pain occurred in only 10·4% of all neonates (TrV: 14·0%, NiV: 10·7%, NoV: 7·6%; $p<0\cdot001$). More frequent assessments of continuous pain occurred in NICUs with pain guidelines, nursing champions, and surgical admissions prompted (all $p<0\cdot01$), and for newborns <32 weeks gestational age, those requiring ventilation, or opioids, sedatives-hypnotics, general anesthetics (O-SH-GA) (all $p<0\cdot001$), or surgery ($p=0\cdot028$). Use of O-SH-GA drugs increased the odds for pain assessment in the TrV (OR:1·60, $p<0\cdot001$) and NiV groups (OR:1·40, $p<0\cdot001$).

Conclusion: Assessments of continuous pain occurred in less than one-third of NICU admissions, and daily in only 10% of neonates. NICU clinical practices should consider including routine assessments of continuous pain in newborns.

Trial Registration: [ClinicalTrials.gov #NCT01694745](https://clinicaltrials.gov/ct2/show/study/NCT01694745).

Key words (5): infant-newborn, infant-premature, suffering, NICU, clinical practices

Key Notes

Why the study was needed

Neonatal pain assessments have previously focused on acute pain associated with skin-breaking procedures, but the importance of assessing continuous pain remains unknown.

What this study found

Assessments of continuous pain varied 0-100% in NICUs, occurring daily in 10·4% of all neonates and at least once during their NICU stay in 31·8% neonates.

Implications for clinical practice or research

In addition to painful procedures, neonatal pain research, clinical guidelines, and bedside practices should also focus on assessments of continuous pain.

Introduction

All newborns experience acute episodic pain or prolonged, continuous pain during admission to neonatal intensive care units (NICUs).(1, 2) Untreated neonatal pain prolongs human suffering, and is often associated with short-term and long-term physical, behavioral, or cognitive sequelae.(3, 4) Conversely, some analgesic drugs can prolong mechanical ventilation,(5) delay feedings,(6) or impair brain growth and development.(7-9) Pain needs to be assessed before treatment, but neonatal pain assessments are time- and labor-intensive, and difficult to implement in routine NICU care.(10-12)

Bedside nurses make global pain assessments or apply validated pain assessment tools before treating a newborn's pain or discomfort,(13, 14) but NICU workloads may not allow bedside nurses to assess pain regularly. Most neonatal pain scales were designed to measure acute pain from skin-breaking procedures, these scales may not be clinically relevant for measuring continuous pain.(15) Assessments of the continuous pain that follows invasive procedures, or inflammation and surgery, will enhance the quality of pain management, avoid untreated pain vs. unnecessary analgesia, prevent under- or over-dosing of analgesics, or developing drug tolerance.(16-18)

Continuous pain may be defined as pain lasting beyond the initial episode that causes tissue injury,(19) mucosal stimulation,(20) or inflammation.(4, 21) Attempts to define chronic or continuous pain in newborns have not led to consistent or clinically useful definitions.(16, 17) Identifying continuous pain is important because it may interfere with

infant growth, prolong hospitalization, alter subsequent pain perception, and impair cognitive and behavioral development.(4, 17) Few methods, however, were designed to assess continuous pain(15, 22-24) and the application of assessment methods designed using acute pain models to clinical assessments of continuous pain remains controversial.(25)

We hypothesized that continuous pain is not assessed routinely during NICU care, but may be assessed more frequently among neonates receiving mechanical ventilation than in neonates breathing spontaneously. Our objectives were to study the frequency of bedside assessments for continuous pain as well as the individual and institutional factors determining the use of these assessments in routine NICU care. We report assessments of continuous pain in 6648 neonates studied in 243 NICUs from 18 European countries.

Methods

Study design

EUROpean-Pain-Audit-In-Neonates (EUROPAIN) was a prospective observational study of clinical practices related to sedation/analgesia and was designed using STROBE guidelines.⁽²⁶⁾ The website (www.europainsurvey.eu) stored multilingual study materials, instructive videos on completing online questionnaires, documents, progress reports, and the complete study protocol (<http://www.europainsurvey.eu/europain-survey-protocol/>). Website links connected authorized users to secure servers (hosting Voozano®[®], Epiconcept, Paris, France) for data entry into standardized questionnaires.

Participating centers

NICU nurses or physicians volunteered as National Principal Investigators (NPIs); each NPI invited participation of all NICUs in their country and provided data on national pain guidelines for neonates. Level-III NICUs initiating and performing the full period of mechanical ventilation were eligible for participation; NICUs unable to provide the full range of Level-III care were not eligible. A study nurse, data quality manager, and physician coordinator were appointed for each unit, providing information on NICU characteristics and local sedation/analgesia protocols. NICUs were queried about the presence of nurses or physicians with specialized knowledge and/or commitment to neonatal pain management; these clinicians were labeled as physician or nurse pain champions.

Data collection

During pre-specified enrollment periods, all NICU admissions up to 44-weeks post-conceptual age were included. Demographic data, modes of ventilation, use of continuous or intermittent sedation/analgesia or neuromuscular blockers, and assessments of continuous pain for each neonate were collected prospectively during the first 28 days of NICU admission, or until death, or hospital discharge. NICUs were specifically asked to record pain assessments performed with pain tools designed for measuring prolonged, continuous pain; two examples of these scales were given (e.g., (EDIN scale, Comfort scale) and staff could record any other pain scales used for continuous pain. Data collection occurred for one month in all participating NICUs; enrollment periods were staggered such that less than forty (40) NICUs enrolled patients concomitantly, allowing the coordinating center to closely monitor data collection. Subject recruitment was authenticated via the NICU admissions log-book. Since the study focus was continuous pain (not procedural pain), we specifically collected data on pain assessments carried out with continuous pain tools, recorded which assessment tools were used, and the number of assessments per day. Newborns were included in the pain-assessed group if at least one assessment of continuous pain occurred during their entire NICU stay. NICUs were included in the pain-assessed group if any assessments of continuous pain were recorded from that unit.

Data quality assurance

A centralized team in Paris monitored completeness and relevance of the data collection. Missing or incongruous data were reported to unit coordinators and locally double-

checked. The monitoring team randomly selected 10% of subjects (minimum 5 patients) and the local data quality manager completely double-checked all these patients. If 1% or more errors occurred, data from another 10% subjects were double-checked; if 1% error rates persisted, all data entries from that NICU were double-checked.

Regulatory compliance

Study protocols and data collection were first approved by the regulatory bodies for Protection of Human Subjects, Data Protection, and Health Research Data Management in France, then approved by similar committees in each country and at some participating sites. Information sheets were given to parents to explain the de-identified data collection and they were free to decline their child's participation. In some countries (e.g. Norway), parents were required to give consent for participation. The study was registered at ClinicalTrials.gov (#NCT01694745).

Sample size

Sample size calculations were based on sedation/analgesia practices.⁽²⁷⁾ We anticipated the participation of at least 15 countries and planned to make comparisons between all countries. We used a χ^2 power analysis to calculate the sample size. We expected small differences in sedation or analgesia practices between countries, estimating an effect size (W) of 0.1 for calculations. NCSS-PASS® (version 2008, Kaysville, UT) showed that a sample size of 2303 neonates would achieve 90% power to detect an effect size of 0.1 with 14 degrees of freedom (15 centres), using a χ^2 test with an α -error of 0.05.

Estimating a small effect size and requiring 90% power ensured adequate sample size, thus minimizing β -error.

Data analyses

Data analyses used SPSS® v17 (Chicago, IL) for descriptive and multivariable analyses. We used a generalized estimating equation (GEE) multivariable model(28) with country or site as the clustering unit. In all neonates, and separately, in ventilated neonates, the clinical factors correlated with NICU pain assessments ($p \leq 0.05$) were included in GEE models. The GEE model fit was assessed by the quasi-likelihood under the independence model criterion (QIC).(29) Results of GEE models are presented as point-estimate odds ratios (OR) with two-sided 95% confidence intervals (C.I.). To assess associations between pain assessments and use of opioids, sedative-hypnotics, or general anesthetics (O-SH-GA), we analyzed data from patient-days with or without O-SH-GA using Mantel-Haentzel χ^2 tests, where modes of ventilation (TrV, NiV) by day were the strata. Two-tailed p-values of 0.05 or less were deemed significant.

Results

Study population

From Oct 1, 2012, to June 30, 2013, we enrolled 6648 neonates eligible for this study (**Figure 1**). Highest levels of ventilation during the study period classified patients into tracheal ventilation (TrV, n=2138), non-invasive ventilation (NiV, n=1493), and spontaneous ventilation groups (NoV, n=3017); patient characteristics are listed in **Table 1** and their distribution among participating countries is listed in **eTable 1** (online data). Guidelines for neonatal pain management were available from 6 countries (33%) and locally, from 182 NICUs (75%). The mean (S.D.) period of study participation was 11·9 (9·7) calendar days. Using data from 78740 patient-days of observation, units reported continuous pain assessment in 2838 neonates. Further detailed analyses showed that 725 neonates had pain assessed only using procedural pain tools and were thus excluded from this analysis.

Clinical practices

Only 2113/6648 neonates (31·8%) received assessments of continuous pain at least once during their NICU stay, with 2 (1-4) (median (IQR)) pain assessments per day (**Table 2**). Continuous pain assessments occurred in the NICU for 984/2138 (46·0%) newborns in the TrV, 523/1493 (35·0%) NiV, and 606/3017 (20·1%) NoV groups ($p<0\cdot001$) (**Table 1**). To correct for the variable numbers enrolled from each country, we weighted the pain assessment rates by the number of enrolled newborns per 10000 births in that country

(**eTable 1**). The weighted pain assessment rates were 36·0% for all infants, 46·6% for TrV, 41·6% for NiV, and 22·3% for NoV groups, showing substantially similar findings.

Daily pain assessments occurred only in 10·4% (689/6648) patients, including 14% TrV patients (300/2138), 10·7% NiV patients (160/1493), and 7·6% NoV patients (229/3017; $p<0\cdot001$). Assessments of continuous pain occurred commonly in French (100%), Dutch (80%), or Belgian (75%) NICUs, but did not occur in five countries. Pain assessments for continuous pain ranged from 6% (Finland) to 90% (France) in the TrV group, from 0% (Germany) to 87% (France) in the NiV group, and from 0% (Germany) to 84% (France) in the NoV group (**Table 2**). On average, individual newborns received 0·8 (Austria and Germany) to 6·7 (Sweden) pain assessments per day (**Table 2**). Moreover, many different tools were used to assess continuous pain; the EDIN (Echelle Douleur Inconfort Nouveau-né) scale was used most frequently (1199/2113, 56·7%); other scores used commonly included the COMFORTneo behavior scale (19·7%), the N-PASS (Neonatal Pain, Agitation, and Sedation Scale; 13·2%), and the Comfort scale (10·1%) (**eTable 2**).

NICU characteristics

NICU characteristics increasing the assessment of continuous pain included the availability of local guidelines, physician or nurse champions, pain consult services, number of surgical admissions and ventilator-days per year (univariable analyses; **Table 3**). Multivariable GEE models using country as a cluster showed that local pain assessment guidelines (OR: 3·96), nurse pain champions (OR: 2·54), and surgical admissions (OR: 1·01) prompted greater use of continuous pain assessments (all $p<0\cdot01$).

Newborn characteristics

In univariable analyses, patient characteristics influencing pain assessments in all neonates were: gestational age, birth weight, outborn status, age at admission, CRIB scores (Clinical Risk Index for Babies), 1-minute and 5-minute Apgar scores, intubation at admission, surgical condition, respiratory distress syndrome, ventilation status, use of O-SH-GA drugs, and hospital length of stay (**Table 4**). Multivariable modeling using NICUs as cluster showed higher odds of pain assessments associated with prematurity (24-29 weeks OR: 1.92; 30-32 weeks OR: 2.11, both $p < 0.001$), intubation at admission (OR: 1.97, $p < 0.001$), need for surgery (OR: 2.14, $p = 0.028$), non-invasive ventilation (OR: 1.88, $p < 0.001$), and use of O-SH-GA drugs (OR: 1.99, $p < 0.001$), but lower odds with inborn status (OR: 0.67, $p = 0.023$) and higher CRIB scores (OR: 0.95, $p = 0.013$) (**Table 4**). More frequent pain assessments occurred specifically on those patient-days associated with tracheal ventilation (42.3% vs. 25.5%, $p < 0.001$), or the use of O-SH-GA drugs (45.6% vs. 26.4%, $p < 0.001$) (**Figure 2**).

Among tracheally ventilated newborns, patient characteristics influencing continuous pain assessments in univariable analyses included outborn status, CRIB scores, 5-minute Apgar scores, intubation at admission, surgical condition, respiratory distress syndrome, use of O-SH-GA, and duration of mechanical ventilation. Multivariable GEE modeling showed that the odds of pain assessments increased with intubation at admission (OR: 2.00, $p < 0.001$) and O-SH-GA use (OR: 1.45, $p = 0.008$), but decreased with higher CRIB scores (OR: 0.93, $p = 0.001$) (**Table 5**).

Are pain assessments associated with sedation/analgesia in ventilated newborns?

In the TrV group, of the 1287 neonates who received O-SH-GA drugs, 660 (51.3%) had at least one pain assessment during their NICU stay. We analysed 33625 patient-days in this group to test for associations between assessments of continuous pain and the use of O-SH-GA drugs. During tracheal ventilation, pain assessment rates on patient-days with and without O-SH-GA use were, respectively, 46.0% vs. 34.7% ($p < 0.001$), with O-SH-GA use prompting 1.60-fold greater odds of pain assessments (95% C.I. 1.48-1.73, $p < 0.001$). When TrV group neonates were not receiving mechanical ventilation, pain assessment rates on patient-days with and without O-SH-GA use were, respectively, 41.7% vs. 24.7% ($p < 0.001$), showing 2.18-fold greater odds of pain assessments (95% C.I. 1.91-2.48, $p < 0.001$) with O-SH-GA use. In the TrV group, 1287 neonates received continuous O-SH-GA drugs; 518 (40.2%) had pain assessments on *the day of* starting O-SH-GA and another 100 (7.8%) had pain assessments on the day *after* starting O-SH-GA drugs.

On analysing 21130 patient-days in the NiV group, rates of bedside pain assessments on patient-days with and without O-SH-GA were, respectively, 36.8% vs. 29.9% ($p = 0.024$) while receiving NiV, and 19.6% vs. 13.9% while not receiving NiV ($p = 0.092$). The odds of continuous pain assessments were 1.40-fold greater (95% C.I. 1.10-1.78) on patient-days associated with O-SH-GA use.

Discussion:

Statement of principal findings

We report the first international, prospective observational study investigating neonatal pain assessment practices in European NICUs. Neonatal pain guidelines recommend routine pain assessments scheduled every 4-6 hours each day,(30, 31) but only 10% of neonates received daily assessments of continuous pain. More than two-thirds of all neonates and more than half of tracheally ventilated neonates received no assessments of continuous pain during their entire NICU stay! This reveals a significant gap between recommended(30, 31) and bedside practices for neonatal pain assessment. Pain assessments varied from 0% to 100% across the three ventilation groups, the 243 NICUs, and the 18 countries, therefore we identified the individual and institutional characteristics associated with pain assessments. We used GEE methods for multivariable analyses to incorporate binary and continuous data, weighted and non-weighted observations, as well as more complex interactions between the variables in our database.(32) NICUs with local pain management guidelines, nursing champions, and increased surgical admissions performed assessments of continuous pain more frequently. Pain assessments also occurred more frequently among newborns less than 32 weeks gestational age, those requiring surgery, mechanical ventilation, use of opioids (morphine, fentanyl, sufentanil), sedatives-hypnotics (midazolam, lorazepam, barbiturates), or general anesthetics (ketamine, propofol) in the NICU. Assessments of continuous pain in ventilated neonates were more likely on the patient-days associated with use of opioids, sedatives/hypnotics, or general anesthetics (Figure 2).

Strengths and weaknesses of this study

Assessments of continuous pain were associated with greater severity of illness, since they occurred more frequently in newborns with extreme prematurity, those requiring intubation at admission, or surgical interventions, or tracheal and non-invasive ventilation during their NICU stay. Neonates with higher CRIB scores, however, had less frequent pain assessments. This discrepancy may occur because the CRIB score was designed to measure risk of mortality from clinical factors at the time of NICU admission(33) and it does not reflect severity of illness during the entire NICU stay.

Pain assessments occurred more frequently following use of O-SH-GA drugs among all neonates, tracheally ventilated neonates, and noninvasively ventilated neonates. Pain assessments were also more likely on the patient-days when these drugs were used (Figure 2). Even among newborns receiving continuous infusions of O-SH-GA drugs, however, only 48% had assessments of continuous pain on the same day or the day after starting these drugs. To limit the data collection burden on participating NICUs, the timing of pain assessments or drug administration were not recorded, therefore our data do not permit more detailed analyses of the relationships between pain assessments and therapeutic decision-making.

Another limitation could be that participating NICUs do not represent national practices in each country. Because of differences in the number of participating NICUs (and subjects) across the different countries (eTable1), we performed sensitivity analyses to weight the pain assessment results with the proportion of neonates enrolled per 10000

live births in each country. The results of these analyses were substantially unchanged, thus suggesting external validity for the European countries participating in this study. While we acknowledge this limitation, other than mandatory data collection (often with suspect quality), we had no practical options to overcome this limitation. Level-III NICUs with relatively high patient volumes participated in all countries, not only representing a snapshot of the most advanced practices in each country, but also allowing us to sample on average about 0·15% of all births per year (eTable 1).

A putative ‘Hawthorne effect’⁽³⁴⁾ could have altered pain assessment practices during study enrollment, but this would be difficult to maintain during 24/7 data collection over a one-month period. Another limitation is that these results were based on documentation of bedside pain assessments. NICU nurses may rigorously record the use of pain medications, whereas pain assessments and non-pharmacological interventions may be recorded less rigorously. Many NICUs require the regular charting of bedside pain scores every 4-6 hours with the patient’s vital signs. Data collection occurred from any existing record, including patient notes, nursing flowsheet at bedside, or other sources. We believe that any pain assessments occurring at the bedside were recorded in our data collection.

Despite the aforementioned limitations, this is the largest study to date, using prospective data collection, robust data quality assurance, enrolling 94% of all eligible neonates, accounting for all non-enrolled neonates, while overcoming the language, cultural, and research regulatory barriers in 18 countries. Thus, it represents the most comprehensive glimpse into the current bedside pain assessment practices in NICUs.

Strengths and weaknesses in relation to other studies

NICU nurses are primarily responsible for bedside pain assessments in neonates although some have questioned the utility(35) and validity(36) of these assessments. An alternative approach calls for using pain scores for research studies and pain detection for clinical care,(37) but it still does not address the need for assessing continuous pain. Well-known weaknesses in the current paradigm for neonatal pain assessments includes their subjectivity, low inter-rater reliability, and other concerns.(10, 18, 38-41) Sedatives and neuromuscular blockers may also mask the behavioral signs of continuous pain.(27) Despite the weaknesses and caveats of neonatal pain assessment tools, we posit that routine assessments of continuous pain will improve individualized pain management.(18, 42)

Of the currently available pain assessment tools, only the EDIN (Échelle Douleur Inconfort Nouveau-Né),(22) COMFORTneo,(24) ALPS-Neo (Astrid Lindgren's Children's Hospital Pain Scale),(23) and the Neonatal Pain, Agitation and Sedation Scale (N-PASS)(43) were designed to assess continuous pain. To develop the EDIN scale, a panel of experts assessed video recordings of neonates with prolonged pain (e.g., necrotizing enterocolitis, postoperative pain) for behavioral indicators of pain (facial activity, body movements, quality of sleep, quality of contact with nurses, consolability). It showed acceptable inter-rater reliability, high internal consistency, and significant differences between painful and non-painful conditions, suggesting preliminary construct validity.(22) van Dijk et al. adapted COMFORT scale to develop the COMFORTneo

scale for newborns with prolonged pain, which appeared to be a promising tool but requires additional studies to support validity and clinical utility.(24) Similarly, Lundqvist et al. adapted the ALPS-1 scale to develop the ALPS-Neo using 5 behavioral parameters, including facial expressions, breathing pattern, limb muscle tone, hand/foot activity, and level of activity to assess continuous pain in neonates.(23) They reported acceptable reliability and face validity, although this tool also requires further validation.(23) The N-PASS was designed to assess pain and sedation in neonates with postoperative pain or mechanical ventilation and showed adequate inter-rater reliability, convergent and discriminate validity,(43) and clinical utility.(44) It was later applied to acute pain with similar results.(45)

Pillai-Riddell et al. interviewed experienced clinicians to define chronic pain in infancy. Their qualitative analysis suggested that: inability to settle, social withdrawal, constant grimacing, tense body, hypo- or hyper-reactivity to acute pain, dysregulated sleep or feeding patterns could serve as potential indicators for chronic pain.(16) Secondary analyses from the NEOPAIN trial suggested that: facial expressions of pain, high activity levels, poor response to handling, and poor ventilator synchronicity were most frequently associated with continuous pain in preterm newborns ≤ 32 weeks of gestation.(15) Though both studies found some overlap with EDIN parameters, they were not used to develop novel assessment tools for persistent pain in neonates.

Although the PIPP and CRIES scales have been tested in settings of postoperative pain, their construct validity as tools to assess continuous pain remains unproven.(25, 46) Our

finding of infrequent assessments of continuous pain is not surprising in the context of few assessment tools available and relative lack of across-the-board validity data for these methods.(18, 42) Furthermore, the validity of these scales when translated into the different languages spoken in the participating countries has not been established.

Meaning of the study

Infrequent and highly variable assessments of continuous pain in newborns may contribute to analgesic complications,(47) oversedation,(48) or tolerance/withdrawal.(49) Given the limitations and controversies reviewed above, the variability noted in this study is not unexpected and mirrors similar findings in adult patients.(50) Our data show that local NICU guidelines and local nurse champions substantially increased the odds for pain assessment, whereas the availability of pain consult services did not (Table 3). All NICUs should develop standardized approaches for neonatal pain and identify experienced nurses to lead this effort. Most NICUs had local neonatal pain guidelines, but only a third of the participating countries had national guidelines. Policymakers at the European Medicines Agency and/or European professional societies should consider developing neonatal pain guidelines for NICUs in all European countries.

Unanswered questions and future research

Neonatal pain research has been focused on the acute episodic pain associated with skin-breaking procedures.(4, 11, 12, 36, 37, 51) We suggest the need for a paradigm shift in neonatal pain research, paying greater attention to prolonged or continuous pain in newborns. First, we need to reach consensus on the taxonomy and definitions of various

pain terms applied to neonates. A preliminary framework to initiate discussions is listed in Table 6. Achieving consensus on these terms may lead to developing newer assessment tools, examining the validity and clinical utility of currently available and novel methods, and using these methods to determine the need for, and the efficacy of therapeutic approaches treating continuous pain in neonates. Neurophysiological approaches,(52) such as near-infrared spectroscopy, electroencephalography, or functional MRI can display pain-induced activity in the brain,(2, 53) whereas skin conductance, heart rate variability, or pupillometry can detect autonomic activity in neonates.(42, 54) If these approaches lead to reliable and clinically useful pain measures, they may allow an independent validation of observer-dependent pain assessment scales for both episodic and continuous pain.

Recent guidelines from American Academy of Pediatrics state that validated pain assessment tools should be used consistently to initiate and monitor the effectiveness of analgesic interventions.(30) Reliable and objective measures of continuous pain in newborns must be defined, developed, extensively validated and used regularly at the bedside, to improve the safety and efficacy of analgesics or other therapies used for treating neonatal pain. By avoiding the acute *and* long-term effects of both unrelieved pain and unnecessary analgesia in newborns, we can optimize sedation/analgesia, improve clinical outcomes, and reduce pain-related suffering in newborns.

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Competing interest statement

All authors have completed the ICMJE uniform disclosure form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

Complete list of abbreviations (listed alphabetically)

Abbreviation	Expanded format
C.I.	confidence intervals
CRIB	Clinical Risk Index for Babies
EDIN	Echelle Douleur Inconfort Nouveau-né

EUROPAIN	EURO pean- Pain-Audit-In-Neonates
GEE	generalized estimating equations
IQR	inter-quartile range
IUGR	intrauterine growth retardation
N-PASS	Neonatal Pain, Agitation, and Sedation Scale
NA	not applicable
NICUs	Neonatal Intensive Care Units
NiV	noninvasive ventilation
NoV	no ventilation, i.e. breathing spontaneously
NPIs	National Principal Investigators
O-SH-GA	opioids, sedative-hypnotics, or general anesthetics
OR	odds ratio
PCA	post-conceptual age
QIC	Quasi-likelihood under the Independence model Criterion
SD	standard deviation
STROBE	ST rengthening the R eporting of OB servational studies in E pidemiology
TrV	tracheal ventilation

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