Sedation/analgesia practices in neonatal intensive care units: Results from the prospective observational EUROPAIN study

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ABSTRACT

Background

Neonates undergoing pain/stress during ICU care frequently receive sedation/analgesia. We determined the current use of sedation/analgesia in 243 European NICUs from 18 countries. Comparative effectiveness research on these practices and the factors associated with them will allow definition of best practices and future clinical trials.

Methods

EUROPAIN (**EURO**pean-**P**ain-**A**udit-**I**n-**N**eonates) is a prospective observational study of sedation/analgesia management in NICU patients. All neonates admitted to NICUs over a 1-month period were included. Data on demographics, modes of respiration, use of continuous or intermittent sedation/analgesia drugs or neuromuscular blockers, pain assessments and drug withdrawal syndromes were collected prospectively during the first 28 days of NICU hospitalization. Multivariable linear regression models and propensity scores were used to assess the association between duration of tracheal ventilation (DTV) and exposure to opioids, and/or sedatives-hypnotics and/or general anesthetics (O-SH-GA).

This study is registered at ClinicalTrials.gov (#NCT01694745).

Findings

A total of 6680 neonates were enrolled with a median (IQR) gestational age of 35.6 (32.0-39.0) weeks gestation, and a birth weight of 2370 (1570-3170) grams. Among the 6680 neonates, 2142 received tracheal ventilation (TV), 1496 non-invasive ventilation (NIV), and 3042 spontaneous ventilation (SV). 2294 (34.3%) infants received sedation/analgesia in continuous infusion, intermittent doses or both, comprising 81.5%, 17.8%, and 9.3% of the

TV, NIV, and SV groups, respectively (p<0.0001). In participating NICUs, 89.3% (70-100% [median rate; IQR]) of TV neonates received sedation/analgesia.

Opioids were given to 1764/6680 (26.4%) and to 1589/2142 (74.2%) in all neonates and in the TV group, respectively. Corresponding figures for midazolam were 576/6680 (8.6%) and 536/2142 (25.0%). 542/2142 (25.3%) neonates in the TV group received neuromuscular blockers including 146 (6.8%) who received them in continuous infusions. Pain assessments were recorded in 58.5%, 45.0% and 30.4% of neonates in the TV, NIV, and SV groups, respectively (p<0.0001).

Among TV neonates, those receiving O-SH-GA required longer DTV (136.2 [173.1] hours) compared to those who did not (39.8 [94.7] hours), p<0.0001.

Interpretation

Three-fourths of TV neonates receive opioids and one-fourth receive midazolam. Wide variations in sedation/analgesia practices occur among NICUs and countries. Widespread use of O-SH-GA among intubated neonates may possibly prolong their need for mechanical ventilation but further research is needed.

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Compelling evidence suggests that all newborns, including those born preterm, respond to pain[1,2]. Repeated neonatal pain leads to poorer cognition[3] and motor function[4], impaired brain development[5,6] and altered pain responses[7]. Since neonatal intensive care unit (NICU) care includes invasive and noninvasive procedures, mechanical ventilation, and medical or surgical conditions causing pain/stress, widespread practices include sedation/analgesia to NICU patients[8]. Recent concerns about the neurotoxic effects of analgesics (including opioids), sedatives and anesthetics on the developing brain[9] have triggered a debate on their potential neuroprotective and neurotoxic effects in the newborn[10]. Very little is known, however, about international sedation/analgesia practices at the bedside. Comparative effectiveness research on these practices and the factors associated with them will allow definition of best practices and future clinical trials.

We sought to describe the current bedside use of sedation/analgesia and neuromuscular blockers in NICUs from 18 European countries and to describe the factors associated with sedation/analgesia use.

Methods

Study design

EUROPAIN (**EURO**pean-**P**ain-**A**udit-**I**n-**N**eonates) is a prospective observational study of sedation/analgesia management in NICU patients, without interfering with routine clinical practices. The study background, objectives and methods in multiple languages, with detailed videos on how to complete on-line questionnaires, all documents and daily progress reports were always accessible through a website (www.europainsurvey.eu ; accessed on July 29th, 2015). All material and documents used or obtained for this study such as protocols in English and national languages, posters, PowerPoint presentations for local teams, announcements,

ethics committee approvals, etc. were always available on the website. Website links connected authorized users to a secure server hosting the application Voozanoo (Epiconcept, Paris, France) for data entry into standardized questionnaires. The report of this epidemiological study follows the STROBE statement[11].

Participating centers

By contacting national neonatal societies and existing networks, we identified a volunteer neonatologist in each country to be the National Principal Investigator (NPI). NPI for each country invited the chiefs of all existing NICUs to participate in this study, with a web-link to the on-line study questionnaires. The letter of invitation was standardized and written in English for all countries. NPIs added to this letter a personal explanation in their national language. Level III NICUs that initiated and performed the full period of tracheal ventilation were eligible, whereas NICUs transferring ventilated newborns to other units were not eligible. In order to avoid distortion of the appraisal of the real management of neonates in intensive care units, pediatric intensive care units that had a NICU activity or area also participated in the study. All centers that agreed to participate identified a nurse and a physician coordinator as well as a data quality manager. Nurse and physician coordinators in each unit provided information to the principal investigators on general statistics and local sedation/analgesia protocols in neonates. The NPI provided data to the principal investigators on national guidelines for neonatal pain management.

Data Collection

All neonates up to 44 weeks of post-conceptional age admitted to the NICU during the enrollment period were included; neonates already in the NICU at the start of the enrollment were not included. We collected for each subject during the first 28 days of hospitalization, or

until death, discharge, or transfer to another hospital prospective data on the demographics, modes of respiration, use of continuous or intermittent (bolus) sedation/analgesia or neuromuscular blockers, performance of pain assessments with any validated tool (a list of tools was available on the data collection form and units could add any other tool they used), and specific practices to treat/prevent drug withdrawal syndromes. Types of ventilation or study medications were collected irrespective of the reasons for their use as long as they were performed or given in the NICU. Medications given prior to NICU admission were not collected. We did not collect data on daily sedation interruptions or vacations nor on the use of sedation scales nor on the type or number of invasive or non-invasive procedures. The exact durations of continuous (ongoing) infusion of sedatives of analgesics were registered; for bolus doses, theirs daily numbers were collected. A neonate was classified in the sedation/analgesia group if he (she) received at least one dose of sedation/analgesia. NICUs recruited patients over a 1-month period, which was considered sufficient to study the practices of all rotating personnel while minimizing temporal changes in clinical practices. Not all the units included patients at the same period. Recruitment periods depended on the completion of regulatory compliances of units, theirs preferences, and the capability of the monitoring team in Paris to follow inclusions. This monitoring team aimed at having no more than 40 units recruiting patients at the same time because the team followed and checked every inclusion. Data were collected on standardized paper questionnaires and then entered on-line or entered directly into the on-line questionnaires. Each unit also kept a logbook of all neonates admitted during the study period.

Data quality assurance

A centralized monitoring team in Paris monitored the completeness of data entered into the study database and identified potential errors by checking the coherence of entered data.

Missing or potentially incongruous data were reported to unit coordinators and locally double-checked. At the end of inclusions, the monitoring team randomly selected 10% subjects (minimum 5 patients) and the local data quality manager completely double-checked these patients. If 1% or more errors occurred, another 10% subjects were double-checked; if error rates of 1% persisted, all data entries from that NICU were double-checked.

Regulatory Compliance

Study protocols and data collection were first approved in France by the regulatory bodies for Protection of Human Subjects, Data Protection, and Health Research Data Management, then approved by similar committees in each country and, if necessary, at each participating site. Information sheets were given to parents to explain the anonymous data collection and they could opt-out of their child's participation. The study was registered at ClinicalTrials.gov (#NCT01694745).

Sample size

We expected the participation of 15 countries and planned to make comparisons among all countries. Sample size was calculated using a chi-square power analysis approach. We expected small differences in sedation/analgesia practices among countries and thus used an effect size (W) of 0.1 for calculations. Using NCSS-PASS 2008 (Kaysville, UT, USA), a sample size of 2303 neonates would achieve 90% power to detect an effect size of 0.1 with 14 degrees of freedom (15 centers), using Chi-Square tests with an α-error of 0.05, see supplemental material for extended explanation.

Data analyses

Data were analyzed with SPSS® v17 (Chicago, IL) for descriptive statistics and with STATA v13 (StataCorp, TX) for multivariable models and propensity scores procedures. In order to determine factors associated with sedation/analgesia use, clinical factors correlated with sedation/analgesia use ($p \leq 0.2$) in the univariate analysis were included in logistic regression models, with stepwise backward elimination of non-significant covariates. Independent variables included country, sex, gestational age, type of respiratory support, severity of illness (Clinical Risk Index for Babies (CRIB) score), age at admission, intrauterine growth retardation, respiratory distress syndrome, 1- and 5-minute Apgar scores, intubation at NICU admission, and assessment with a pain tool. Since data were clustered, p-values and confidence intervals were adjusted using a robust sandwich estimator. Results of regression analyses are presented as point estimate Odds Ratios (OR) with two-sided 95% Confidence Intervals (C.I.). An internal validation of the logistic model was performed using a bootstrap approach with 1000 samples.

Since there is concern about the prolongation of invasive ventilation by the use of opioids, sedatives and anesthetics in the neonate, we assessed, in tracheally intubated infants, the association between exposure to opioids and/or sedatives-hypnotics and/or general anesthetics (O-SH-GA), and duration of tracheal ventilation. All covariates associated ($p<0.20$) with duration of tracheal ventilation (DTV) in univariate analyses were included in multivariable linear regression models to assess this association. Because infants were not randomly assigned to receive O-SH-GA, we used propensity scores to reduce the effect of treatment-selection bias and potential confounders in this observational study. The propensity score for an individual is the probability of being treated conditionally based on the individual's covariate values[12]. A logistic regression model was used to create the propensity score as a function of the variables associated with the use of O-SH-GA. Infants treated and not treated

with O-SH-GA but with similar propensity for receiving O-SH-GA treatments were matched. Matching was performed, after randomly ordering infants, using the psmatch2 algorithm[13] in STATA with 1 to 1 nearest neighbor matching without replacement and with maximal caliper distance of 0.125 times the propensity score standard deviation (SD). The covariate imbalance and its correction between the O-SH-GA treated and untreated groups was measured visually and by using absolute standardized differences to compare the groups. Standardized differences up to 10% are considered inconsequential[14]. Using matched pairs, we compared DTV between infants treated or not treated with O-SH-GA. In the population of all tracheally ventilated neonates, two other techniques using the propensity score, stratification and regression adjustment, confirmed the analyses conducted in matched pairs[12]. Stratification based on propensity score quintiles divided the tracheally ventilated group into five strata. Within each stratum, infants treated or not treated with O-SH-GA were compared. Previous research found that this technique removes up to 90% bias caused by confounding variables[12]. To further adjust for confounders, two multivariable linear regression models predicting DTV were constructed; one including only the propensity score and O-SH-GA treatment status as independent variables and another one including these variables plus all variables significantly associated with DTV in univariate analyses. Since the rate of mortality can have an effect on DTV, we used the number of ventilator-free days (VFD) as a secondary endpoint to estimate the effect of the use of O-SH-GA. This outcome is largely used in the intensive care unit (ICU) litterature[15]. VFD was defined as the number of calendar days from the time of tracheal extubation to day 28 after NICU admission. If a neonate was reintubated and subsequently extubated prior to day 28, VFDs were counted from the end of the last period of tracheal intubation. If a neonate was receiving TV on day 28 or died prior to day 28, VFDs were zero[15]. For neonates discharged before day 28 of admission, VFDs were zero if the neonate was still intubated at dicharge (transfer) and VFDs were counted from the time of

tracheal extubation to day 28 after NICU admission if the neonate was already extubated at discharge. VFDs were compared with the paired-sample Wilcoxon Rank Test. Two-tailed P-values of 0.05 or less were considered significant.

Role of the funding source

The funders of the study had no role in the design of the study, data collection or analysis, interpretation of data, writing of the report, or in the decision to submit the paper for publication. RC had full access to all the data in the study, at study completion, and had final responsibility for the decision to submit for publication.

Results

Study population

From October 1st, 2012 to June 30th, 2013, 243 NICUs from 18 European countries enrolled 6680 neonates (Figure S1, Table S1). Table S1 shows, for each country, how representative participating units were of all eligible units. Six countries (33%) had national guidelines and 182 units (74.9%) reported local protocols for neonatal sedation/analgesia. Table 1 A shows patient demographics and clinical characteristics. The mean (SD) gestational age and birth weight were, respectively, 35.0 (4.6) weeks gestation, and 2384 (1007) grams. The mean (SD) length of study participation was 11.9 (9.7) calendar-days and the observation period represented 79,185 patient-days. Since there is an important concern of sedation/analgesia in very preterm neonates, we also present the patient demographics and clinical characteristics of the subgroup of infants less than 33 weeks gestation in Table 1 B.

The highest level of ventilation during the study period classified patients into three groups: tracheal ventilation (TV, n=2142), non-invasive ventilation (NIV, n=1496), and spontaneous ventilation (SV, n=3042), (Tables 1 A and 1B). A surgical operation requiring a consulting specialist (different from invasive bedside procedures) during the study period was reported for 99/2142 (4.6%) neonates in the TV group. Compared to NIV and SV groups, neonates in TV group had lower gestational age, birth weight, rates of birth in the study hospital and Apgar scores, and higher age at admission and disease severity scores (CRIB). In the TV group, 62.7% and 71.2% of all gestational ages and of those under 33 weeks gestational age, respectively, were already intubated at NICU admission, Tables 1 A and B.

Use of analgesia and sedation

Of the 6680 infants enrolled, 2294 (34.3%) infants received, at least once, sedation/analgesia drugs administered by continuous infusion, intermittent (bolus) doses or both, comprising 81.5%, 17.8%, and 9.3% of the TV, NIV, and SV groups respectively ($p<0.0001$). The median (IQR) rates of sedation/analgesia use by the 243 NICUs for all neonates and for TV neonates were 33.3% (18.5%-56.5%) and 89.3% (70%-100%) respectively.

We quantified the use of opioids, sedatives-hypnotics, general anesthetics, and NSAIDs, local anesthetics and others in each of the ventilation groups (Tables 1A and 1B). The detailed list of all drugs used by ventilation group is shown on Table S2. Opioids included mainly morphine (given to 43.1%, 2.5% and 1.8% of neonates of the TV, NIV and SV groups, respectively) , fentanyl (29.4%, 2.7% and 0.8%), and sufentanil (10.3%, 0.1% and 0.2%); sedatives-hypnotics included mainly midazolam (25.0%, 1.1% and 0.8%), chloral hydrate (3.9%, 1.1% and 0.4%) and phenobarbital (2.5%, 0.5% and 0.6%); general anesthetics included mainly ketamine (5.6%, 0.6% and 0.2%) and propofol (2.8%, 0.3% and <0.01%);

Nonsteroidal Anti-inflammatory Drugs included acetaminophen (24.7%, 11.5% and 6.6%) and ibuprofen (0.7%, 0.1% and <0.01%). Opioids were given to 1764/6680 (26.4%) and to 1589/2142 (74.2%) in all neonates and in the TV group, respectively; corresponding figures for sedatives-hypnotics were 786/6680 (11.8%) and 690/2142 (32.2%), and for general anesthetics 199/6680 (3.0%) and 178/2142 (8.3%). Midazolam was given to 576/6680 (8.6%) and to 536/2142 (25.0%) in all neonates and in the TV group, respectively (Table 1A). Figures 1A, 1B, and 1C show the mode of administration of, respectively, all sedation/analgesia drugs, all opioids, and all sedatives-hypnotics in the tracheal ventilation group by country. Tables S3A, S3B, S3C show, by country, the main analgesics, sedatives-hypnotics and neuromuscular blockers used in the TV, NIV, and SV groups, respectively.

Morphine was administered to 923/2142 (43.1%), 37/1496 (2.5%), and 56/3042 (1.8%) neonates in the TV, NIV and SV groups respectively. Figure 2 shows the mode of administration of commonly used opioids, midazolam, propofol, chloral hydrate, ketamine, and acetaminophen. Figure S2 shows the continuous infusion durations of main opioids, midazolam and neuromuscular blockers in the TV, NIV and SV groups. Propofol was given to 59 (2.8%), 5 (0.3%), and 1 (<0.01%) neonates in the TV, NIV, and SV groups, respectively. It was always administered as a bolus. In the TV group, 542 (25.3%) neonates received neuromuscular blockers, including suxamethonium (205 [9.6%]), atracurium (115 [5.3%]), pancuronium (82 [3.8%]) and other drugs. Neuromuscular blockers were given exclusively as boluses in 396 (18.5%) neonates; only 146 (6.8%) received them in continuous infusions. The median (IQR; range) duration of neuromuscular blockers infusion was 33.9 (13.4-65.9; 0.2-422.0) hours. Neuromuscular blockers were given to 183/779 (23.5%) of the 24-29 weeks gestational age, 76/360 (21.1%) of the 30-32, 95/389 (24.4%) of the 33-36, and 187/613 (30.5%) of the 37-42, respectively (p=0.003). All neonates who received

neuromuscular blockers received some form of O-SH-GA. Bedside assessments with a pain tool were recorded in 1250/2138 (58.5%), 672/1493 (45.0%) and 916/3017 (30.4%) neonates in the TV, NIV, and SV groups, respectively ($p<0.0001$). From the 2838 neonates who had a pain assessment with a tool, the EDIN scale was used in 1200 (42.3%) of them, the Comfort Behavior in 416 (14.7%), the N-PASS in 279 (9,8%), the Comfort Scale in 213 (7.5%), the PIPP score in 139 (4.9%), the NIPS in 113 (4.0%), the Pain Assessment Tool in 101 (3.6%), the CRIES scale in 45 (1.6%), and others in 636 (< 1%).

Opioids, sedatives-hypnotics or general anesthetics in tracheally ventilated neonates

From the 2142 neonates in the TV group, 1674 (78.2%) received O-SH-GA including 1634 (76.3%) who received opioids and/or midazolam. Out of the 2142 neonates in this group, 1290 (60.2%) received O-SH-GA in continuous infusions. From the 451 (21.1%) neonates who had sedation/analgesia exclusively as boluses, 382 (17.8%) received O-SH-GA. Most of those who received O-SH-GA boluses had very few boluses; only 91 (4.2%) received 4 boluses or more and 28 (1.3%) 10 boluses or more of O-SH-GA. In fact, 199 (9.3%) neonates received only 1 or 2 bolus of O-SH-GA exclusively on the day of a tracheal intubation. The reasons for bolus administration were not recorded.

Sedation/analgesia by patient-day in TV neonates

The 2142 neonates of the TV group accounted for 33715 patient-days of observation including 12638 with TV and 21077 without TV (days before intubation or after extubation). Use of opioids and sedatives differed in patient-days with and without TV. Opioids were used continuously and/or in bolus in 7960/12638 (63.0%) patient-days with TV and in 807/21077 (3.8%) patients-days without TV, $p <0.0001$. Corresponding figures for sedatives were

2744/12638 (21.7%) and 320/21077 (1.5%), p <0.0001 and in particular for midazolam 2196/12638 (17.4%) and 114/21077 (0.5%), p <0.0001.

Practices to treat or prevent drug withdrawal syndromes

Opioids or benzodiazepines were given to 1640/2142 (76.6%), 99/1496 (6.6%), and 105/3042 (3.5%) and weaned gradually in 641/1636 (39.2%), 30/97 (30.9%), and 43/103 (41.7%) neonates of the TV, NIV, and SV groups respectively (p=0.22). A drug withdrawal scale was used during the study period in 153/1640 (9.3%), 11/99 (11.1%) and 27/105 (25.7%) of neonates treated with opioids/benzodiazepines from the TV, NIV and SV groups, respectively (p<0.0001); of note, 24 of the 27 SV group neonates who had an assessment with a drug withdrawal scale were born to drug-addicted mothers. From the 191 neonates who had a withdrawal assessment with a tool, the Finnegan scale was used in 107 (56.0%) of them, the Lipsitz in 33 (17.3%), the Withdrawal Assessment Tool-1 (WAT-1) in 8 (4.2%), the Opioid and Benzodiazepine Withdrawal Scale in 7 (3.7%),and other scales in 39 (20.4%). From the neonates who received opioids/benzodiazepine, a drug withdrawal syndrome was diagnosed in 69/1640 (4.2%), 4/99 (4.0%), and 21/105 (20.0%) neonates, and treated/prevented in 111/1640 (6.8%), 9/99 (9.1%) and 24/105 (22.9%) from the TV, NIV, and SV groups respectively (p<0.0001). The most common medications used to treat/prevent a drug withdrawal syndrome were morphine 84/144 (58.3%), clonidine 37/144 (25.7%), phenobarbital 14/144 (9.7%), methadone 10/144 (6.9%), lorazepam 5/144 (3.5%), diazepam 4/144 (2.8%), and others 26/144 (18.1%).

Factors associated with sedation/analgesia use

Sedation/analgesia usage varied from 0% to 100% among centers. Tables 2 A and 2 B show factors determining the use of any sedation/analgesia and the use of O-SH-GA in all neonates

and TV neonates. Bootstrap internal validation of the models indicated very little optimism bias (less than 0.0005 for all models). Thus, the optimism-corrected receiver operating characteristic (ROC) curves were practically the same as the original apparent ROC curves; see tables 2A and 2B. Factors driving greater sedation/analgesia use in all neonates included ventilation status, higher CRIB scores and bedside pain assessments, whereas preterm birth and younger age at NICU admission (<72 hours) promoted less frequent use of sedation/analgesia. Among TV neonates, O-SH-GA use was driven by higher CRIB and bedside pain assessments, whereas very preterm birth, younger age (<7 hours) and being already intubated at NICU admission diminished O-SH-GA use.

Association of the use of opioids, sedatives-hypnotics or general anesthetics and the duration of tracheal ventilation

Among TV neonates, tracheal ventilation in those treated or not treated with O-SH-GA lasted for 136.2 (173.1) and 39.8 (94.7) hours, respectively ($p<0.0001$). A multivariable linear regression model adjusted for country, age at admission, sex, gestational age, intubation status at admission, CRIB and Apgar scores, intrauterine growth retardation, respiratory distress syndrome, and bedside pain assessments showed that O-SH-GA use was associated with longer DTV (Table 3).

Using variables listed on Table 2 A, propensity scores were calculated for 2004/2142 (93.6%) TV infants, including 1559 (77.8%) who received O-SH-GA and 445 (22.2%) who did not. Propensity score matching yielded 427 pairs of infants who did or did not receive O-SH-GA and eliminated previous differences in covariates (Figure 3 and Table S4), yet showed several-fold increases in TV duration associated with O-SH-GA use [mean (SD) 149.0 (183.6) vs. 38.2 (88.5); median (IQR; range) 77.3 (25.5-169.8; 0.5-669.0) vs. 12.5 (5.8-28.9;

0.1-658.4) hours, p<0.0001]. Within the propensity score quintiles, O-SH-GA use was associated with significantly longer DTV within each stratum (Table S5 and Figure S3). Two additional multivariable linear regression models (one including propensity score and O-SH-GA treatment status as independent variables; another including these variables plus all variables associated with DTV in univariate analyses) also showed that O-SH-GA use was associated with longer DTV. Furthermore, since in practice the use of O-SH-GA may be the consequence of long tracheal ventilation, we identified among the 427 matched pairs those in whom the start of continuous infusion of O-SH-GA was within 6 hours of the start of tracheal ventilation. We found 228 such pairs and again although there were not significant differences in baseline and clinical characteristics between the groups with and without O-SH-GA, the duration of tracheal ventilation was longer in neonates who received O-SH-GA. In this subgroup of 228 pairs, the mean (SD) and median (IQR; range) duration of tracheal ventilation for infants with and without O-SH-GA, respectively, were 128.1 (162.4) vs 40.1 (93.9) hours and 73.1 (25.5-144.5; 1.0-669.0) vs 12.2 (5.8-32.2; 0.1-658.4) hours. These results were consistent with the inverse approach analysis using the number of ventilator-free days. The median (IQR) of VFDs for neonates with and without O-SH-GA, respectively, were 22 (9-26) and 26 (25-27), p<0.0001.

Discussion

We report a prospective, multicenter, international study documenting around-the-clock bedside practices of sedation/analgesia in European NICUs. Our study cohort was representative of NICU populations in Europe and other developed countries with the participation of 18 countries, uniformity of data collection, and >90% inclusion rates in 16/18 countries. One-third of NICU admissions and four-fifths of tracheally ventilated neonates received some sedation/analgesia. In the TV group, three-quarters received opioids and a

fourth received midazolam, although wide variations existed among centers and countries in the frequency and type of neonatal sedation/analgesia. The use of sedation/analgesia varied from 0% to 100% among centers.

Sedation/analgesia practices in the NICU population were previously documented in two declarative national surveys[16,17] and one cross-sectional survey[18]. Swedish NICUs declared that they used pharmacological analgesia during mechanical ventilation but reported no information on the type or frequency of drugs used[16]; 36% of Italian NICUs reported routine use of opioids for mechanical ventilation[17]. A survey conducted in 1993-1994 in 14 Canadian NICUs found that 21.3% of neonates received analgesia and/or anesthesia during a 1-week study period[18]. Two prospective studies explored sedation/analgesia practices in pediatric ICUs (PICUs)[19,20]. Among PICU patients (aged >28 days to 18 years) receiving neuromuscular blockers, 72% received sedatives and 70% received opioids[19]. Another prospective study of 338 critically ill children in 20 British PICUs reported the use of 24 different sedative/analgesic agents[20]. Their study population included 39 neonates of whom 90% received morphine and 36% received midazolam. Surveys and practice audits evaluating the uptake of sedation/analgesia guidelines in adult ICUs have been published and reviewed[21]. A review of 20 surveys[21] published from 1999 to 2009 found that only two were prospective, one national survey[22] was designed to study sedation/analgesia in ventilated adults and another international survey[23] was designed to study mechanical ventilation, not analgesia/sedation. From 2010 to 2015, we found 15 surveys including only two national prospective studies, one from Canada[24] and another one from Chile[25], dealing with sedation/analgesia practices in adult ICUs. One study[26] in the United States concerned a retrospective single-center cohort and the other studies were based on declarative questionnaires mainly on the use of written local procedures, sedation, analgesia, sedation scales, and on the modalities of drug administration.

NICU care includes a stressful environment[27], numerous painful procedures[28], invasive and noninvasive mechanical ventilation[28,29], and various neonatal diseases or surgical interventions promoting sedation/analgesia in the NICU[8]. Given that for the last 30 years it has been accepted that neonates are capable of feeling pain[1] and that evidence supports the notion that all neonates are conscious living beings[30], a humane approach that includes prevention/treatment of neonatal pain is considered an ethical obligation[31]. This approach is further substantiated by associations between higher pain exposure and adverse developmental outcomes[5,32,33]. While guidelines for procedural pain management in neonates are published[34,35], none exist for prolonged sedation/analgesia in the NICU, perhaps explaining the current heterogeneity of clinical practices.

We found that 26.4% of all neonates and 74.2% of TV neonates received opioids. In the TV group, 60.2% of neonates received continuous infusions of O-SH-GA. Although, we did not record the exact reasons of O-SH-GA administration, these continuous infusions were very likely given with the purpose of providing sedation/analgesia during tracheal ventilation. Surgery, which was a potential reason for the use of O-SH-GA, was reported in only 4.6% of neonates of the TV group. This rate may seem low; the authors hypothesize that probably many NICUs did not have a neonatal surgical team in the same hospital and thus transferred their surgical neonates to surgical units in other hospitals. We did not collect information on this organizational aspect. It is also very likely that O-SH-GA administered exclusively as boluses were given mainly for invasive procedures and less for sedation/analgesia during tracheal ventilation; only 4.2% and 1.3% of neonates in the TV received 4 boluses or more, and 10 boluses or more, respectively. Of note, most (62.7% of all gestational ages and 71.2% of those less than 33 weeks gestational age) of the neonates in the TV group were already

intubated at NICU admission. This is consistent with the fact that tracheal intubation is both a marker of illness severity and a common reason for NICU admission. Given the high rate of infants born in the same hospital as the NICU, most of these tracheal intubations were likely performed in the delivery room. Since we did not collect data on medications used prior to NICU admission, we ignore whether any sedation/analgesia was used for tracheal intubation, any other procedure or mechanical ventilation prior to NICU admission. Although this information would have been worth to know, the aim of our study was to determine sedation/analgesia practices in the NICU; furthermore, we felt that the collection of data by third party staff who did not participate in the study entailed the risk of lower reliability. We do not know the effects that sedation/analgesia medications that may have been used prior to NICU admission potentially had on our results, in particular for neonates intubated prior to NICU admission; nonetheless, the propensity score matching, as described below, aimed at removing bias created by baseline characteristics. Opioid use for ventilated neonates has been endorsed by arguments including developmentally regulated pain sensitivity, clinical instability from acute pain/stress, unsynchronized breathing and suboptimal ventilation[36], or long-term effects on brain development[37-40]. A Cochrane review concluded that opioids reduce neonatal pain scores, and do not prolong ventilation, alter mortality or subsequent intelligence, motor function, or behavior[37], but that insufficient evidence supports routine opioid therapy for ventilated newborns. Despite that recommendation, wide variations exist in the patterns of opioid use in European countries. Sufentanil, for example, was mostly used in France and Poland, despite limited data supporting its use[41]. Another review concluded that remifentanil and fentanyl are more effective than morphine for tracheal intubation[42]. Notwithstanding the above arguments endorsing the use of opioids in the tracheally ventilated neonates, one fourth of such neonates in this study did not receive any opioid. We speculate that this may be explained, in part, by the fact that the use of morphine neither improved

neonatal neurodevelopmental outcomes[43], nor provided adequate analgesia for procedural pain in TV preterms[44]. Health providers also fear that opioid use may prolong the length of tracheal ventilation. Nonetheless, we should keep in mind that alleviation of neonatal pain and suffering is a *per se* reason to use adequate analgesics, including opioids, in this population. In this study, one fourth of TV neonates who did not receive O-SH-GA were ventilated for more than 28.9 hours and one for at least 658.4 hours. Overall, midazolam was by far the most common sedative used. It was given to 25.0% of neonates who underwent TV and its use varied from 0% to 72% among European countries (Table S3), despite lack of (pre)clinical data supporting midazolam sedation for neonates[45,46]. Dexmedetomidine, which is frequently used for sedation in the adult ICU, was not used at all in our participating neonates. A recent phase II/III study has shown that dexmedetomidine is effective for sedating preterm and full-term neonates and is well-tolerated without significant adverse effect[47]; preterm neonates had decreased plasma clearance and longer elimination half-life.

Consistent with previous studies, logistic regression analyses showed independentassociations of sedation/analgesia with ventilation status, pain assessment[48], and severity of illness[49]. Contrary to a systematic review and meta-analysis published in 2010[37] stating that opioid exposure did not have an effect on the duration of tracheal ventilation in the neonate, in our study O-SH-GA exposure was associated with prolonged ventilation among tracheally ventilated neonates. Additional multivariable analyses (propensity score matching, stratification, regression adjustment) and analyses on infants in whom O-SH-GA were started early after initiation of tracheal ventilation substantiated this finding, consistent with recent randomized trials and drug-related respiratory depression[49-51]. Propensity score matching allowed to eliminate observed differences in baseline characteristics between infants who received O-SH-GA and those who did not. Potential confounders such as, for instance, being

on tracheal ventilation at NICU admission were balanced by this approach. The rates of infants already intubated at admission in those who received O-SH-GA and in those who did not were, respectively, 58.8% and 80.2% ($p<0.0001$) before matching and 76.6% and 79.4% ($p=0.325$) after matching, Table S4. Similarly, illness severity as assessed by the CRIB score was not statistically different after matching, Table S4. Also, since the use of O-SH-GA could be the consequence of prolonged tracheal ventilation and not its cause, we confirmed on a subgroup of matched pairs in whom the start of continuous infusion of O-SH-GA was within 6 hours of the start of tracheal ventilation that the duration of tracheal ventilation was longer in neonates who received O-SH-GA. Neonatal brains are also deficient in P-glycoprotein, required for actively extruding sedatives/analgesics from the brain[52], thus increasing their respiratory depressant effects. Delayed excretion of sedation/analgesia drugs, particularly in preterm neonates[53], may also lead to respiratory depression. Further, after initiating O-SH-GA use in tracheally ventilated neonates, some clinicians may not discontinue this therapy until the newborn is ready for extubation or already extubated[54]. Among the TV neonates who received O-SH-GA, 25% received these drugs for more than 5 to 7 days (Figure S2A), placing them at greater risk for tolerance, withdrawal syndromes, and iatrogenic injury[55]. Limited information exists for other O-SH-GA drug classes, although their effects on neonatal respiratory drive may be similar to opioids. Using non-pharmacological therapies, or analgesics without respiratory depressant effects for treating neonatal pain/stress could avoid this outcome[56].

The rates of pain assessments were relatively low: 58.5%, 45.0% and 30.4% in the TV, NIV, and SV groups, respectively. This is worrisome because pain assessment should currently be considered standard of care. It was very surprising to find out that units that used frequent O-SH-GA did not always accompany this practice with pain assessments. However, it should be

also mentioned that neonatal pain assessment is not an easy task and that the existence of numerous scales may be confusing[57]. More research is needed on the implementation of pain scales at the bedside and on the ways of optimizing neonatal pain management with pain assessments. Regarding drug withdrawal practices, opioids or benzodiazepines were weaned gradually in 39.2%, 30.9%, and 41.7% of neonates in the TV, NIV, and SV groups respectively. This practice is consistent with current recommendations. The American Academy of Pediatrics (AAP) has considered reasonable, that each clinical unit establish a threshold level of cumulative exposure to opioids and benzodiazepines above which drug dependency can be expected to occur with a likelihood that justifies anticipatory initiation of a weaning protocol. For example, setting a threshold at a cumulative fentanyl exposure of >2 mg/kg or >7 days' duration would predict a likelihood of dependency >50% but <100%[58]. Infants with a cumulative exposure to opioids or benzodiazepines below the thresholds for initiation of weaning protocols can undergo a rapid taper of these medications over a 24- to 48-hour period; those above the thresholds may need weaning periods of up to 2 to 3 weeks[58]. The AAP also recommends that signs of drug withdrawal be scored by using a published abstinence assessment tool. Infants with confirmed drug exposure who are unaffected or demonstrating minimal signs of withdrawal do not require pharmacologic therapy. Although different medications were used to treat/prevent drug withdrawal syndromes in this study, morphine was the most commonly used. The limited available evidence from controlled trials of neonatal opioid withdrawal supports the use of oral morphine solution and methadone when pharmacologic treatment is indicated; growing evidence suggests that oral clonidine is also effective either as a primary or adjunctive therapy, but further prospective trials are warranted[58].

Interpretation of our results must be tempered by some limitations. First, the participation of eligible units varied widely among countries and may not represent each country's practices. In most countries, however, numerous large NICUs providing advanced NICU care participated and allowed us to sample on average about 0.15% births (Table S1). Second, we cannot exclude a "Hawthorne effect", with altered bedside practices during study enrollment. However, data collection extending 24/7 over a period of 28 days may have minimized this tendency. Third, as a trade-off between study design and protocol compliance, we did not record the doses of sedation/analgesia medications used for neonates. Requiring these data would have created massive burdens on the NICU staff, lowering our participation rate in each country, or protocol compliance within each NICU, or increasing the rates of missing or incomplete data. For the same reasons, we did not record the purposes for the use of sedation/analgesia. Thus, we ignore how often these medications were used for mechanical ventilation or for invasive procedures. The epidemiology of invasive procedures in the NICU has already been reported[28]. Fourth, our models of the factors associated with the use of sedation/analgesia may be subject to bias because neonates were classified on an ever/never sedation/analgesia basis. This gives subjects who received occasional sedation/analgesia the same weight as those who received frequent and long-lasting sedation/analgesia. Finally, we cannot exclude a potential bias in the association found between the use of O-SH-GA and longer duration of tracheal ventilation using the propensity score approach. Although propensity score techniques can balance observed baseline covariates between exposure groups, they cannot balance unmeasured characteristics or unknown confounders. One could hypothesize that illness severity, not measured by the CRIB score, is still a potential confounder. Thus, as with all observational studies, propensity score analyses have the limitation that remaining unmeasured confounding may still be present.

We report that one-third of NICU admissions and four-fifths of tracheally ventilated neonates received some sedation/analgesia with wide variations in practices among different NICUs and different countries. We found that the use of opioids, sedatives-hypnotics or general anesthetics in the NICU may be associated with longer durations of tracheal ventilation. These data underline the need to develop international guidelines for judicious use of sedation/analgesia in the NICU, to investigate the therapeutic and adverse effects of these drugs in neonates, and to develop newer, safer approaches for sedation/analgesia in this vulnerable population.

Panel: Research into context

Systematic review

A Medline search using the words "pain", "newborn", "sedation" and "analgesia" in different combinations with no time limits, and a cross-reference search of found articles yielded only three studies that briefly included, among other objectives, the assessment of general sedation/analgesia practices in the NICU population. Two were declarative national surveys[16,17] and one a cross-sectional survey[18]. Swedish NICUs declared that they used pharmacological analgesia during mechanical ventilation but reported no information on the type or frequency of drugs used[16]; 36% of Italian NICUs reported routine use of opioids for mechanical ventilation[17]. A survey conducted in 1993-1994 in 14 Canadian NICUs found that 21.3% of neonates received analgesia and/or anesthesia during a 1-week study period[18]. Most other epidemiological studies assessed procedural pain management or particular situations (post-operative, mechanical ventilation during chronic lung disease, necrotizing enterocolitis) in the NICU. Regarding the clinical effects of the use of opioids, sedatives-hypnotics or general anesthetics in tracheally ventilated neonates, a search in the Cochrane database yielded 2 systematic reviews on the use of opioids[37] and on the use of midazolam[45]. The

former included 10 studies that reported the duration of tracheal ventilation during treatment with opioids. A meta-analysis of six studies showed no significant effect of opioid administration on the duration of tracheal ventilation[37]. The latter reviewed studies on intravenous midazolam infusion for sedation of infants in the NICU in order to determine whether midazolam infusion is an effective sedative and to assess clinically significant short- and long-term adverse effects associated with its use[45]. Three trials were included in the review. Among other effects, a statistically significant longer duration of NICU stay was found in the midazolam group compared to the placebo group. No data on the duration of tracheal ventilation were reported.

Interpretation

To our knowledge, this is the first prospective, multicenter, international study documenting around-the-clock bedside practices of sedation/analgesia in European NICUs. Our study cohort was representative of NICU populations in Europe and other developed countries with the participation of 18 countries, uniformity of data collection, and >90% inclusion rates in 16/18 countries. The inclusion of 2142 tracheally ventilated neonates and the wide variety of observed practices allowed a robust identification of factors associated with the use of sedation/analgesia in these infants and a detailed analysis of the association between the use of opioids, sedatives-hypnotics or general anesthetics and the duration of tracheal ventilation. Contrary to previous studies[37], opioids, sedatives-hypnotics or general anesthetics exposure was associated with prolonged ventilation in tracheally ventilated neonates. We found that one-third of NICU admissions and four-fifths of tracheally ventilated neonates received some sedation/analgesia with wide variations in practices among different NICUs and different countries. Three-fourths of tracheally ventilated neonates receive opioids and one-fourth receive midazolam.

The wide variations in sedation/analgesia practices among different NICUs and different countries in this study and the association of the use of opioids, sedatives-hypnotics or general anesthetics with longer durations of tracheal ventilation underline the need to develop international guidelines for judicious use of sedation/analgesia in the NICU, to investigate the therapeutic and adverse effects of these drugs in neonates, and to develop newer, safer approaches for sedation/analgesia in this vulnerable population.

Contributors

RC, ME, and KJSA were responsible for the study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtaining funding; and study supervision. EC was responsible for the acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; and study supervision.

LB, HL were responsible for obtaining funding; interpretation of data; and critical revision of the manuscript for important intellectual content.

EB, AAA, RA, KS, TPo, CM, PL, TPa, SAM, MI, SS, RT, BO, AB, AD, MS were responsible for acquisition of data and critical revision of the manuscript for important intellectual content.

Declaration of interests

All authors declare no competing interests.

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