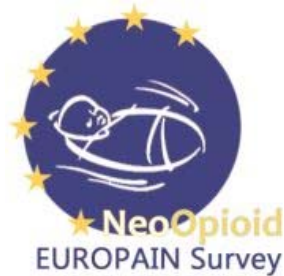


Confidential document



EUROPAIN (EUROpean Pain Audit In Neonates)

**European survey of sedation and analgesia practices for newborns
admitted to intensive care units**

Version: V5

Date: February 28, 2012

Principal Investigators:

Last name, First name: Carbajal, Ricardo

Address: Emergency Department, Trousseau University Hospital, Paris,
France

26, av du Dr Netter, 75012 Paris, France

Telephone: +33 144736487

Fax: +33 144736985

Email: ricardo.carbajal@trs.aphp.fr

Last name, First name: Erikson, Mats

Address: Centre for health care sciences, Örebro University Hospital, S-701
85 Örebro, Sweden

Telephone: +46 70 5926676

Fax: +46 19 611 38 18

Email: mats.eriksson@orebroll.se

National Investigators:

TABLE OF CONTENTS

| | |
|--|----------|
| OUTLINE OF THE EUROPAIN STUDY IN THE NATIONAL LANGUAGE..... | 3 |
| 1.1 BACKGROUND AND RATIONALE | 3 |
| 1.2 MAIN OBJECTIVE | 4 |
| 1.3 PRINCIPAL CRITERIA..... | 4 |
| 1.4 SECONDARY OBJECTIVES AND CRITERIA..... | 5 |
| 1.5 TYPE OF STUDY | 5 |
| 1.6 STUDY PLAN..... | 5 |
| 1.7 JUSTIFICATION OF NUMBER OF PATIENTS..... | 6 |
| 1.8 MAIN ACTIONS CARRIED OUT DURING THE STUDY | 6 |
| 1.9 EXPECTED RESULTS AND POTENTIAL IMPLICATIONS..... | 7 |

OUTLINE OF THE EUROPAIN STUDY IN THE NATIONAL LANGUAGE

1.1 Background and rationale

The alleviation of pain is a basic and human right regardless of age. Neonates do feel pain and it has been shown that preterm infants are even more vulnerable to pain than older infants. The more vulnerable preterm neonates are precisely those that are more exposed to pain. Neonates admitted to intensive care units, both neonatal intensive care unit (NICU) and pediatric intensive care unit (PICU), undergo dozens or even hundreds of painful procedures during their stay. These painful procedures include, for many of the ICU neonates, a tracheal intubation followed by mechanical ventilation. The pain and stress that are induced by mechanical ventilation as well as by repetitive procedures or painful diseases has led medical staff to use sedation and analgesia in neonates admitted to intensive care units. The subjectivity and difficulty inherent to pain measurement in neonates have probably contributed to a wide variety of neonatal sedation and analgesia practices. To date, these practices have been rarely studied.

Why would sedation and analgesia be necessary?

Mechanical ventilation is a potentially painful intervention. Adults often describe mechanical ventilation as a painful and anxiety-provoking experience. The main objectives of sedation and analgesia are: reduction of pain, stress and irritability, promotion of blood pressure stability, promotion of ventilator synchrony and improvement of oxygenation. In the long term, reduced stress, as well as reduced fluctuations in oxygenation and blood pressure is believed to minimize the risks of neurological injury and death. However, the use of sedation and analgesia is only conceivable in the respect of the principle that must accompany all medical actions: *first, do no harm*.

Pain and stress undergone during the neonatal period can have deleterious short-term and long-term consequences. Some of these consequences have been reduced with adequate analgesic treatment. Current data show the necessity to give adequate sedation and analgesia to ventilated neonates.

Statements promoting the use of sedation and analgesia

The increased awareness that neonates feel pain, the ethical obligation to treat this pain with analgesics, the growing body of evidence demonstrating that untreated neonatal pain can lead to altered reactivity to pain that persists throughout infancy and childhood as well as the need for a humane management of neonates have led to the development of International and National Guidelines promoting the use of analgesics in the neonatal population. These Guidelines state that units that provide neonatal care should develop and implement guidelines concerning neonatal pain. However, the existing literature is still conflicting regarding the use of sedation and analgesia for ventilated neonates. Current data indicate that there is insufficient evidence to recommend the routine use of opioids in mechanically ventilated newborns and that opioids should be used selectively. Sedation and analgesia in non-ventilated babies is extremely rare.

CONFIDENTIAL DOCUMENT**Practices across Europe and USA**

Data on sedation and analgesia practices in ventilated neonates are very rare. In 1995 the SOPAIN study carried out in the United States showed that factors predicting the use of on-going analgesia and sedation in neonates included: mechanical ventilation, higher gestational age, and male gender. In 2005, the French EIPPAIN study showed that the rate of continuous sedation and analgesia was 69.6% in ventilated neonates with large variations among centers (16.7% to 90.9%). The most frequently used drugs were midazolam and morphine.

To date, there are no data permitting the comparison of neonatal pain management within the European countries. The availability of these data will enable comparison of practices with state-of-the-art knowledge.

Study Hypothesis

The EUROPAIN study is an epidemiological study that is based on the following hypothesis:

- Most newborn ventilated infants receive continuous sedation and analgesia.
- Non ventilated babies are not sedated.
- Morphine, fentanyl and midazolam are the most frequently drugs used in this setting.
- Infrequent use of validated pain assessment tools to monitor sedation and analgesia occurs in ventilated newborn infants.
- Most units have developed written local guidelines for sedation and analgesia in ventilated neonates, but huge variability exists among practitioners in the same unit, across different units in the same country, and across different countries in Europe.
- Development, dissemination, and regular updates of common European standards will improve the care and clinical outcomes of ventilated newborn infants.

1.2 Main objective

- To determine the current clinical practices regarding the use of sedative and analgesic drugs for ventilated newborns in different countries in Europe.

1.3 Principal criteria

- The frequency of ventilated neonates receiving sedation and analgesia in different European units
- The medications used for sedation and analgesia in ventilated neonates across Europe.

CONFIDENTIAL DOCUMENT

- The length of use of medications administered for sedation and analgesia in ventilated neonates
- Similarities and differences in sedation and analgesia practices among European countries

1.4 Secondary objectives and criteria

- To determine the proportion of neonatal units that have developed and implemented local written guidelines to provide continuous sedation and analgesia in ventilated newborn infants as well as to prevent and treat procedural pain.
- To document the published guidelines for neonatal analgesia and sedation in different European countries and develop consensus for common European standards that can be applied in all medical settings.
- To determine the frequency of use of pain assessment tools in ventilated newborn infants and evaluate their impact on pain management practices.
- To determine practices to assess and prevent withdrawal syndromes.

Secondary criteria

- Variations across European countries of the proportions of units that have developed and implemented local written guidelines for sedation and analgesia in ventilated neonates
- Identification and description of national guidelines for sedation and analgesia in neonates in all participating countries. Identification of recommended drugs.

1.5 Type of study

- Epidemiological observational study.

1.6 Study plan

The EUROPAIN STUDY is observational and therefore it will not interfere with routine practices of participating units. No changes in diagnostic, therapeutic or any managing strategy of patients are imposed by the participation in this study. This epidemiological study will only collect data on clinical practices in each unit.

The inclusion criteria are:

- All neonates up to a corrected age of 44 weeks post conception. That means, for example, that a baby of 40 weeks gestational age can be included up to 28 days (4 weeks) of post natal age or that a baby of 32 weeks gestational age can be included up to 12 weeks of post natal age.

CONFIDENTIAL DOCUMENT**At the unit level**

- No modifications of current managing protocols or strategies are required by the participation in the EUROPAIN STUDY. The unit coordinators will only provide data on local protocols to manage procedural pain and sedation and analgesia in neonates as well as on general statistics of the unit. All treatments are authorized for included neonates since this study does not include any intervention
- A nurse and physician coordinator as well as a data quality manager will be designated for each unit.

At the national level

- The country coordinator will provide data on national guidelines to treat or prevent procedural or continuous pain in neonates.

Data collection

- The duration of data collection for every included infant is 28 days. However, data collection will stop before 28 days if the infant leaves the unit (discharge, death, transfer to another hospital).
- Data will be collected on individual data collection forms. These forms include demographic data, modes of respiration, continuous or intermittent sedative, analgesic or neuro-blocking drugs, pain assessment and drug withdrawal practices.
- Paper patient data collection forms are written in English with a subtitled translation in the country language. The web-based databases display questionnaires in the country language.
- The data collection forms will be completed by the unit nurse or physician coordinator or the person that they will designate.
- For each center, the duration of the inclusion period will be one month.
- Data will be entered on a secure web-based questionnaire.

1.7 Justification of number of patients

Regarding the number of neonates to include in order to show possible differences in sedation and analgesia practices among the participating European countries, we have considered a scenario where differences are small. Thus, we have chosen an effect size (W) of 0.1. We have also assumed that 15 countries will participate. Using NCSS-PASS 2008 software, we have found that a total sample size of 2303 neonates will achieve 90% power to detect an effect size (W) of 0.1 using a 14 degrees (15 centers) of freedom Chi-Square test with a significance level (α) of 0.05. Therefore, we aim at including an average of 154 neonates per participating country.

1.8 Main Actions carried out during the study

- In each country, the National Principal Investigators (NPI) will send invitations to join the study to all level 3 neonatal units of the country. The NPI will then communicate the names, emails and telephone numbers of the units that accept to participate to the EUROPAIN STUDY principal investigators

CONFIDENTIAL DOCUMENT

- The NPI is responsible for the coordination of all units in the country and ensures communication with the EUROPAIN STUDY principal investigators
- The NPI will collect demographic data about the participating country.
- A nurse and physician coordinator as well as a data quality manager will be designated for each unit. The nurse and physician coordinator are responsible for informing all the unit staff about the study.
- The EUROPAIN STUDY principal investigators have prepared a specifically designed web-based database to enter data. Data can be entered directly from the patient's file. A paper copy of this database will be distributed to allow centers that prefer to perform a preliminary entry on paper forms before entering data on the web-based database. The medical coordinator or a person that he (she) will choose will enter the data into these specifically designed databases.
- The physician coordinator will report general statistics of the unit such as number of beds, number of admission, year ventilator-days etc to the Europain study principal investigators.
- Every unit will also report existing local guidelines on sedation and analgesia in ventilated infants, including routines for withdrawal and on the use of pain assessment tools.
- MONITORING PANEL. A monitoring panel will be created to monitor the progress of the study. This panel will ensure communication with all the participating units. This monitoring panel will be constituted by two persons working full-time during the study period. They will be stationed in Paris and working under the responsibility of EUROPAIN STUDY principal investigators.

1.9 Expected results and potential implications

According to our working hypothesis we expect to find that most ventilated newborns infants receive continuous sedation and analgesia in European units. However, we feel that important differences among units within a country and among countries will appear. These differences will very likely also exist in the development of written local guidelines. This study will also reveal the differences among countries concerning the type of analgesics and sedatives used for ventilated neonates. Currently, we do not have these data. The neonatal network created by this study as well as the dissemination of the EUROPAIN STUDY results will allow the improvement of neonatal pain management in Europe. The availability of these data will enable comparison of practices with state-of-the-art knowledge.