Neonatal Pain Management is not the same During Days and Nights in Intensive Care Units

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004086
Article Type:	Research
Date Submitted by the Author:	20-Sep-2013
Complete List of Authors:	Guedj, Romain; AP-HP - Hôpital Armand Trousseau, Service d'urgences pédiatriques; Inserm U-953, Danan, Claude; Centre Hospitalier Intercommunal de Creteil, Unité de réanimation néonatale Daoud, Patrick; Centre Hospitalier André Grégoire, Réanimation Infantile Zupan, Véronique; AP-HP, Hôpital ANtoine Béclère, Pédiatrie et Réanimation néonatale Renolleau, Sylvain; AP-HP, Hôpital Armand Trousseau, Réanimation Néonatale et Pédiatrique Zana-Taieb, Elodie; Médecine néonatale Port-Royal-Cochin, NICU Aizenfisz, Sophie; AP-HP, Hôpital Robert Debré, Réanimation pédiatrique Lapillonne, Alexandre; Université Paris descartes, AP-HP, Hôpital Necker-Enfants Malades, Réanimation néonatale de Saint Blanquat, Laure; Hôpital Necker, PICU Granier, Michele; Hôpital sud-francilien, NICU Durand, Philippe; Bicetre Hospital, Paediatric Intensive Care Unit Castela, Florence; Hôpital Poissy, Unité de réanimation néonatale Coursol, Anne; CH René Dubos, NICU Hubert, Philippe; Hopital Necker Paris, intensive care unit Cimerman, Patricia; Hopital Armand Trousseau, Centre National de Ressources de lutte contre la Douleur Anand, Sunny; Le Bonheur Children's Hospital, University of Tennessee Health Science Center Khoshnood, Babak; Hopital Saint Vincent de Paul, INSERM U953 Carbajal, Ricardo; Hôpital Trousseau, Service des Urgences Pédiatriques
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Intensive care
Keywords:	NEONATOLOGY, after hour care, painful procedures, Pain

Neonatal Pain Management is not the same During Days and Nights in Intensive Care Units

Authors : Romain Guedj[1], MD, Claude Danan[2], MD, Patrick Daoud[3], MD, Véronique Zupan[4], MD, Sylvain Renolleau[5], MD, PhD, Elodie Zana[6], MD, Sophie Aizenfisz[7], MD, Alexandre Lapillonne[8], MD, PhD, Laure de Saint Blanquat[9], MD, Michèle Granier[10], MD, Philippe Durand[11], MD, Florence Castela[12], MD, Anne Coursol[13], MD, Philippe Hubert[14], MD, PhD, Patricia Cimerman[15], Research Nurse, Babak Khoshnood[16], PhD, KJS Anand[17], MD, PhD, Ricardo Carbajal[18], MD, PhD.

[1] Inserm U-953, 75020 Paris ; AP-HP, Hôpital Armand-Trousseau, Service d'urgences pédiatriques, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

M.D.

[2] Centre Hospitalier Intercommunal de Créteil, Unité de réanimation néonatale et soins intensifs, 40 avenue de Verdun 94010 Créteil Cedex, France

M.D.

[3] Centre HospitaIier André Grégoire, Réanimation infantile, 56, bd de la Boissiere 93105 Montreuil-sous-Bois Cedex, France

M.D.

[4] AP-HP, Hôpital Antoine Béclère, Pédiatrie et Réanimation Néonatale, 157, rue de la Porte de Trivaux 92141 Clamart cedex, France

M.D.

[5] AP-HP, Hôpital Armand-Trousseau, Réanimation Néonatale et Pédiatrique, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

PhD

[6] Maternité Port-Royal, Réanimation néonatale, 123 boulevard Port Royal, 75014 Paris, France

M.D.

[7] AP-HP, Hôpital Robert Debré, Réanimation et Surveillance continue pédiatrique, 48 boulevard sérurier 75019 Paris, France

M.D.

[8] Université Paris Descartes, AP-HP, Hôpital Necker-Enfants Malades, Réanimation Néonatale, 149 rue de Sèvres 75015 Paris, France

Ph.D

[9] AP-HP, Hôpital Necker-Enfants Malades, Réanimation Polyvalent Pédiatrique, 7149 rue de Sèvres, 75015 Paris, France

M.D.

[10] Centre Hospitalier Sud Francilien, Médecine Néonatale, 116 boulevard Jean Jaurès, 91100 Corbeil, France

M.D.

[11] AP-HP, Hôpital Bicêtre, Réanimation Néonatale et Pédiatrique, 78 rue du général Leclerc, 94275 Kremlin-Bicêtre, France

M.D.

[12] Centre Hospitalier Intercommunal, Hôpital Poissy, Unité de Réanimation Néonatale, 23 boulevard Gambetta, 78100 Poissy, France

M.D.

[13] Centre Hospitalier René Dubos, Médecine Néonatale et Réanimation Pédiatrique, 6 avenue de l'Ile de France, 95303 Pontoise, France

M.D.

[14] AP-HP, Hôpital Necker-Enfants Malades, Réanimation Polyvalent Pédiatrique, 149 rue de Sèvres, 75015 Paris, France

PhD

[15] AP-HP, Hôpital Armand-Trousseau, Centre Nationale de Ressources de lutte contre la Douleur26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

RN (Research nurse)

[16] Inserm U953, Maternité Port-Royal, , 123 boulevard Port Royal, 75014 Paris, France

PhD

[17] University of Tennessee Health Science Center & Le Bonheur Children's Hospital, Memphis, TN

PhD

[18] Inserm U-953, 75020 Paris ; AP-HP, Hôpital Armand-Trousseau, Service d'urgences pédiatriques, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France; Université Pierre et Marie Curie, 75006 Paris

PhD

Corresponding author : Romain GUEDJ, Service des urgences pédiatriques, Hôpital Trousseau, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12

Phone: + 33 144 736 487 Fax: +33 144 736 985

Email : romainguedj@gmail.com

Abbrévations :

NICU : Neonatal intensive care unit

OR : Odd ratio

PICU : Pediatric intensive care unit

Key words :

Pain ; Neonate ; Neonatology and infant care ; After-hours care ; painful procedures ; pain

Word count : 2492 words.

Abstract

Objective : To determine whether analgesic use for painful procedures performed in neonates in the Neonatal intensive care unit (NICU) differs during nights and days and during each of the 6-hour period of the day.

Design : Conducted as part of the prospective observational EPIPPAIN study which was designed to collect in real time and around-the-clock bedside data on all painful or stressful procedures

Setting : 13 NICUs and PICUs in the Paris Region, France.

Participants: All 430 neonates admitted to the participating units during a 6-week period between September 2005 and January 2006.

Data collection. During the first 14 days of admission data were collected on all painful procedures and analgesic therapy. The five most frequent procedures representing 38012 of all 42413 (90%) painful procedures were analyzed.

Intervention : Observationnal study

Main outcome assesment : We compared the use of specific analgesia for procedures performed during each of the 6-hour periods of a day: Morning (7:00AM to 12:59PM), Afternoon, Early Night and Late Night, and during Daytime (Morning+Afternoon) and Nighttime (Early Night+Late Night).

Results: 7724 out of 38012 (20.3%) painful procedures were carried out with a specific analgesic treatment. For Morning, Afternoon, Early Night and Late night, respectively, the use of analgesia was 25.8%, 18.9%, 18.3% and 18%. The relative reduction of analgesia was 18.3%, $p<0.001$, between Daytime and Nighttime and 28.8%, $p<0.001$, between Morning and the Rest of the day. Parental presence, nurse 8-hour shifts and written protocols for analgesia were associated with a decrease in this difference.

Conclusion : The substantial differences in the use of analgesia around-the clock may be questioned on quality of care grounds.

Article summary :

Article focus : Some epidemiological studies focused on mortality-risk and medical errors raise concern about the homogeneity of care around the clock. Variation of analgesic use for painful procedure in neonates in intensive care units during day has never been studied.

Key messages : Specific analgesia for paiful procedures was more frequent during daytime than nighttime. It gradually decreased from morning to late night. Pain management guidelines should include standardization of care across 24 hours.

Main strenghts and limitations of this study : This is the first prospective multicenter study to show variations in analgesic practices around-the clock. The around the clock variations in analgesia use for procedural pain management did not correspond to an isolated practice of a single center but rather to the practices of a large geographical region.

Patients and their families expect that the same quality of care be provided to patients 24 hour-a-day. In reality, some epidemiological studies, mainly focused on mortality-risk and medical errors have found poorer outcomes for hospital care given during evening or night-time hours[1–7]. Among neonates, one study reported that perinatal mortality rates fluctuated according to the hour of birth with a peak occurring in the evening[3] and another study found a higher mortality for term neonates born in the evenings, nights or weekends[4]. These studies raise concern about the homogeneity of care in settings where patients expect safe and high quality care 24 hour-a-day. Significant practice variability also occurs in many other aspects of care. To our knowledge, the variation of neonatal pain management during day and night shifts has not been studied yet.

Neonatal pain management has received much attention during the last two decades leading professional societies to issue guidelines to improve pain management in this vulnerable population[8,9]. These guidelines highlight the necessity to improve analgesia for invasive procedures, which constitute the main source of pain in sick or premature infants admitted to the neonatal intensive care unit (NICU). However, surveys of clinical practices suggest that many evidence-based interventions have not been applied effectively in NICUs[10] and that wide gaps exist between knowledge and practice[11]. The undertreatment of pain in this population would be aggravated by variations in analgesic use according to the time of the day. Thus, the question about variation of quality of pain management during day and night is of practical relevance.

We designed this study to determine whether analgesic use for painful procedures performed in neonates in the NICU and the Pediatric intensive care unit (PICU) differs during nights and days and during four 6-hour periods of the day. This study was conducted as part of the EPIPPAIN study[12].

METHODS

Study centers

The detailed methodology of the EPIPPAIN study was published elsewhere [12]. EPIPPAIN was a prospective observational study designed to collect 24-hours a day bedside data on all painful or stressful procedures performed in neonates admitted to NICUs and PICUs of a geographically defined region. All 14 tertiary care centers, NICUs and PICUs in the Paris Region were invited to participate and 13 accepted the invitation.

All the participating units had developed their pain management protocols locally. No instructions were given to modify the standard of care for procedural pain management in neonates. The study protocol and the data collection forms were reviewed by the local committee for the protection of human subjects.

Study population

We included in this study all neonates admitted to the participating units during a 6-week period between September 2005 and January 2006. Inclusion criterion was admitted preterm neonates younger than 45 postconceptional weeks and term neonates younger than 28 days. There were no exclusion criteria.

Data collection

During the first 14 days of admission to the participating units, prospective data were collected on all neonatal procedures causing pain, stress, or discomfort with the corresponding analgesic therapy. Specific pre-procedural analgesia included nonpharmacological (eg, sweet solutions, sucking) or pharmacological treatments (eg, single- or multiple drug doses). Nursing and medical staff at the bedside recorded all procedures on a specific form in real

time. Since the EPIPPAIN study did not include data about the characteristics of the participating units, we conducted a phone survey with each head nurse in March 2010. Since the EPIPPAIN study did not include data about the characteristics of the participating units, we conducted in March 2010 a phone survey with each head nurse present at the time of the initial study (2005-2006). We inquired about nurse shifts (two or three per day), shift rotation (between day and night), existence of a pain coordinator, written standardized protocols for sucrose analgesia, parental presence authorized 24-hours a day, ratios of residents to number of beds in order to describe the teaching status [13], and existence of a night head nurse.

Painful procedures

The EPIPPAIN study collected data on 430 neonates who underwent 60969 procedures. Because the current international definition of pain [14] does not apply to neonates, we chose a published empirical approach to define pain. Of these 60969 procedures, 42413 were considered painful, including 44 different procedures. In order to study the differences in analgesic management during the 24 hours of the day, we selected the five most frequent procedures that would both be readily performed at any time in an intensive care unit and also represent the majority of painful procedures : nasal or tracheal suctioning, heel sticks, adhesive removals, and vascular punctures (arterial punctures, venipunctures and intravenous cannulas). As shown in figure 1, these five procedures accounted for 90% of all painful procedures.

The use of procedural analgesia was defined as the use of specific analgesia given prior to painful procedures (pharmacological or nonpharmacological therapy).

Data analysis

Data were double entered into a relational database (EpiData Entry, version 3·0, Odense, Denmark) and analyzed with SPSS, v14 for Windows, (SPSS Inc, Chicago, Illinois) and Stata

v.10.0 software (Stata Corporation, College Station, TX, USA). Procedures were distributed according to the time when they were performed, into four 6-hour periods: Morning (from 7:00AM to 12:59PM), Afternoon (from 1:00PM to 6:59PM), Early Night (from 7:00PM to 0:59AM) and Late Night (from 1:00AM to 6:59AM). We also defined Daytime as Morning + Afternoon and Nighttime as Early Night + Late Night. These timings were chosen because in France most of the day and night nurse shifts start at 7:00am and 7:00pm, respectively. Descriptive statistics were used to summarize continuous and categorical variables.

We calculated the percentage of use of specific analgesia for each of the 6-hour periods, Daytime, Nighttime and for the period including Afternoon + Early Night + Late Night. The use of specific analgesia was compared between periods using Chi2-tests.

We included in our model procedures and children characteristics that were found to be associated with the use of specific analgesia prior to procedures in the EPIPPAIN study (Day of procedure, mechanical ventilation, parental presence, continuous analgesia, surgery, sex, and gestational age) and variables describing centers (nurse shift, nurse rotation, pain coordinator, written protocols for sucrose analgesia, policy on parental presence authorized 24-hours, night head nurse and teaching status). In order to investigate factors associated with differences in analgesia use 24-hours a day, we tested the interactions between analgesia use and the characteristics of newborns, centers, and procedures. Since data were not independent, procedures were clustered by child and center. We used a multilevel logistic regression model with random intercept and slope in order to adjust interactions, to test cross level interactions and to control for confounding factors[15,16]. In this multilevel analysis, procedure, child and center were at the lowest, second and highest level, respectively.

All the described factors were included in our model and all interactions between time of procedures (daytime or nighttime) and each covariate were obtained. Results are presented as

point estimate odds ratios (ORs) with 2-sided 95% confidence intervals (CI). The threshold for statistical significance was set up at a probability value of <0.05.

RESULTS

From the 430 neonates included in the study, 309 (71.9%) were from NICUs and 121 (28.1%) from PICUs. The mean (SD) length of stay was 8.4 (4.6) calendar days and the observation period represented 3598 patient-days. The overall rate of mechanical tracheal ventilation was 70.5%, but it varied from 46.2% to 92% across units. Table 1 lists the demographic characteristics of the study population and Table 2 lists the characteristics of the participating centers. Figure 2 shows the distribution of painful procedures by hour of the day.

Specific Analgesic treatments

Overall, 7724 out of 38012 (20.3%) painful procedures were carried out with the provision of a specific analgesic treatment. Regarding heel sticks and vascular punctures, 3696/8396 (44.0%) and 1483/2088 (71.0%), respectively, were performed with specific analgesia. Analgesic treatment varied widely among centers. Table 3 shows the use of specific analgesia, by center, for all procedures, heel sticks and vascular punctures.

Analgesia use according to time of the day

Figure 3 shows the use of analgesia for each 6-hour period of the day. For all painful procedures or for skin-breaking procedures, the use of analgesia was higher in the morning, decreased during the day and was lowest in the late night (p<0.001).

For all procedures taken together or for skin breaking procedures analyzed separately, the use of analgesia was significantly higher for procedures performed in the morning versus the rest

of the day, p<0.001, as well as for procedures performed during the daytime versus the nighttime, p<0.001, Table 4.

Clinical Factors associated with Diurnal Variations in Analgesia

Interactions between differences in analgesia use during daytime and nighttime and the characteristics of children, centers and procedures in univariate analysis are listed in Table 5. We can see for instance that regarding mechanical ventilation the relative reduction in analgesia use during nighttime compared to daytime was 13.1% in invasively ventilated infants and 20.8% in spontaneously breathing or non-invasively ventilated infants.

The inclusion of all clinical factors in a multilevel analysis, showed that analgesia use was significantly higher for procedures performed during the daytime versus the nighttime, (OR = 2.11[1.18–3.78], p< 0.05). In this multilevel model, day of procedure (related to admission), mechanical ventilation, parental presence, nurse shift, and written protocol for analgesia significantly interacted with time of procedure, as shown in table 6.

DISCUSSION

This is the first prospective multicenter study to show variations in analgesic practices around-the clock. The use of specific analgesia for painful procedures was more frequent during daytime than nighttime. Moreover, we found that specific analgesia for painful procedures was the highest in the morning and the lowest in the nighttime. In fact, it gradually decreased from morning to late night.

The relative reduction in the use of specific analgesia between daytime and nighttime was 18.3% for all five painful procedures and this difference reached 28.8% between the morning and the rest of the day. Such substantial differences in the use of analgesia may be questioned on quality of care grounds. We consider that the lower use of analgesia during those periods

represents a marker of poor quality care that needs to be overcome. The differences in analgesia use between daytime and nighttime that we found in this study were independent of the type of procedure and whether the procedure was more frequently performed during a period of the day. In fact, heel sticks were homogeneously distributed around-the clock and vascular punctures were more frequent during the morning, but the differences in analgesia use were very similar and consistent (figure 3).

The around the clock variations in analgesia use for procedural pain management did not correspond to an isolated practice of a single center but rather to the practices of a large geographical region. The participation of all but one center in this region, the uniform data collection at all centers, and 100% patient inclusion during the study period ensure that the study cohort was representative of NICU procedural pain management in the Paris region. Moreover, we feel that these results could be extrapolated to the entire French territory because this is the most populated region of France and it closely reflects the practices in the rest of the country.

The variation of quality of neonatal care over the day has been rarely studied directly. Most studies have used outcomes as a proxy to assess this variation. Some studies reported increased rates of perinatal death at night[3–5]. Although mortality could be considered as an important proxy to assess quality of care, it has the disadvantage of being related to only serious or critical conditions and it is exposed to several confounding factors. Medication error rate has also been used in a few studies to assess variations in quality of care. It has been found that errors were higher during nighttime than during daytime(6, 20). However, care quality cannot be restricted to a safety problem. Optimal care quality implies, among other

standards, care without pain. Thus, analgesic use for painful procedure is also a parameter to measure care quality.

In an attempt to explain our findings, we investigated factors associated with differences of analgesia use around-the-clock. Parental presence, nurse 8-hour shifts and written protocols for analgesia decreased the difference of analgesia use between day and night. These results suggest that written protocols or parental presence may limit the reduction of analgesia use during nighttime. Protocols limit the freedom of health care providers about the management of pain, making the practice of caregivers more homogeneous. It has been reported that the presence of protocols, by harmonizing practices, increases the quality of care[10]. Similarly, it has been reported that the presence of parents influences the practice of caregivers[17]. Our data also suggest that shorter hour shifts (8-hour) for nurses decrease the difference of analgesia use between day and night. In other health care areas, it has been shown that 12-hours shifts negatively influence the behavior of care providers yielding to less efficient care[18,19]. However, the area of variations in pain management practices is highly complex and to attempt to explain it by staffing or protocols is probably simplistic. Other factors that we have not studied could play a role. Contextual factors may influence staff behaviors. Although number of nurses is homogeneous during daytime and nighttime in French NICUs, more medical staff is around in the morning and in the afternoon. Interprofessional collaboration practices[20] and higher access to personnel to care for complex patients[21] may enhance pain practices. Thus, analgesic use may also be influenced by the total number of staff and not only nurses.

We acknowledge two limitations of this study. First, a potential bias would be a difference in quality of data collection during days and nights. We consider that this is not likely because we ensured a completeness of reporting by verifying from the patients' charts that all procedures were documented on the study datasheets. Furthermore, there is no reason that a nurse recorded a procedure but not the use of analgelsia. Second, we collected data about the characteristics and organization of center in a retrospective manner 5 years after the collection of clinical data. This might have introduced a bias. However, we feel that this bias was minimized because we obtained data from the head nurse who usually keeps records of all organizational details. Since we only had 13 centers, data about organizational characteristics should be looked upon with caution.

CONCLUSION

Our findings suggest that the constant efforts to improve care quality should also include standardization of care across 24 hours and pain management guidelines should reinforce this message. The variation of care quality during the day is certainly a complex phenomenon that deserves further research. It appears that human factors intervene in the process of care delivery and we need to better understand them in order to improve care quality. Our results suggest that the modification of organisational factors such as parental presence and written protocols may contribute to the homogenization of quality of care around the clock.

Aknowledgment

We would like to aknowledge l'Académie de Médecine

REFERENCES

1 Duke GJ, Green JV, Briedis JH. Night-shift discharge from intensive care unit increases the mortality-risk of ICU survivors. *Anaesth Intensive Care* 2004;**32**:697–701.

2 Laupland KB, Shahpori R, Kirkpatrick AW, *et al.* Hospital mortality among adults admitted to and discharged from intensive care on weekends and evenings. *J Crit Care* 2008;**23**:317–24.

3 Paccaud F, Martin-Béran B, Gutzwiller F. Hour of birth as a prognostic factor for perinatal death. *Lancet* 1988;**1**:340–3.

4 Pasupathy D, Wood AM, Pell JP, *et al.* Time of birth and risk of neonatal death at term: retrospective cohort study. *BMJ* 2010;**341**:c3498.

5 Stephansson O, Dickman PW, Johansson ALV, *et al.* Time of birth and risk of intrapartum and early neonatal death. *Epidemiology* 2003;**14**:218–22.

6 Miller AD, Piro CC, Rudisill CN, *et al.* Nighttime and weekend medication error rates in an inpatient pediatric population. *Ann Pharmacother* 2010;**44**:1739–46.

7 Hendey GW, Barth BE, Soliz T. Overnight and Postcall Errors in Medication Orders. *Academic Emergency Medicine* 2005;**12**:629–34.

8 Anand KJ. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med* 2001;**155**:173–80.

9 Prevention and management of pain and stress in the neonate. American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee. *Pediatrics* 2000;**105**:454–61.

10 Sharek PJ, Powers R, Koehn A, *et al.* Evaluation and development of potentially better practices to improve pain management of neonates. *Pediatrics* 2006;**118 Suppl 2**:S78–86.

11 Spence K, Henderson-Smart D. Closing the evidence-practice gap for newborn pain using clinical networks. *J Paediatr Child Health* 2011;**47**:92–8.

12 Carbajal R, Rousset A, Danan C, *et al.* Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA* 2008;**300**:60–70.

13 Aiken LH, Clarke SP, Sloane DM, *et al.* Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. *JAMA* 2002;**288**:1987–93.

14 Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. *Pain* 1979;**6**:249.

15 Merlo J, Chaix B, Ohlsson H, *et al.* A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *J Epidemiol Community Health* 2006;**60**:290–7.

16 Merlo J, Chaix B, Yang M, *et al.* A brief conceptual tutorial on multilevel analysis in social epidemiology: interpreting neighbourhood differences and the effect of neighbourhood characteristics on individual health. *J Epidemiol Community Health* 2005;**59**:1022–8.

17 Johnston C, Barrington KJ, Taddio A, *et al.* Pain in Canadian NICUs: have we improved over the past 12 years? *Clin J Pain* 2011;**27**:225–32.

18 Borges FN da S, Fischer FM. Twelve-hour night shifts of healthcare workers: a risk to the patients? *Chronobiol Int* 2003;**20**:351–60.

19 Macias DJ, Hafner J 2nd, Brillman JC, *et al.* Effect of time of day and duration into shift on hazardous exposures to biological fluids. *Acad Emerg Med* 1996;**3**:605–10.

20 Latimer MA, Johnston CC, Ritchie JA, *et al.* Factors affecting delivery of evidence-based procedural pain care in hospitalized neonates. *J Obstet Gynecol Neonatal Nurs* 2009;**38**:182–94.

21 Stevens B, Riahi S, Cardoso R, *et al.* The influence of context on pain practices in the NICU: perceptions of health care professionals. *Qual Health Res* 2011;**21**:757–70.

Table 1. Demographic characteristics of 430 neonates

Characteristics	Number (%)	Mean (SD)	Median (IQR)	Range
Gestational age group at birth 24-29 wk 30-32 wk 33-36 wk 37-42 wk	 119 (27.7) 108 (25.1) 84 (19.5) 119 (27.7)			
Birth weight (g)		1962 (957)	1743 (1155-2738)	490-4760
Male	237 (55.1)			
Inborn (born at study hospital)	237 (55.1)			
Age at admission (h)			2.5 (0.5 – 24.0)	
Surgery during the study period	30 (7.0)			
Mechanical tracheal ventilation	303 (70.5)			
Duration of participation (d) Overall 24-29 wk 30-32 wk 33-36 wk 37-42 wk	 	 8.4 (4.6) 11.6 (3.8) 8.7 (4.6) 6.6 (4.0) 6.0 (3.9)	 8.0 (4.0-14.0) 14.0 (9.0-14.0) 9.0 (4.0-14.0) 6.0 (3.0-9.0) 5.0 (3.0-8.0)	 1-14 2-14 1-14 2-14 1-14
Hospitalized for more than 14 days	126 (29.3)			
Died during the study period	24(5.6)			

Table 2: Characteristics of centers

	Number of centers n = 13
Nurse shift	
2 per day	9
3 per day	4
Day-night nurse rotation	
Yes	7
No	6
Pain coordinator	
Yes	10
No	3
Written standardized protocols for sucrose analgesia	
Yes	11
No	2
Parental presence authorized 24-hours	
Yes	6
No	7
Teaching status*	
Minor	6
Major	7
Night head nurse	
Yes	2
No	11

* postgraduate trainees /bed ratio : minor teaching units if ratios were ¼ or less, major teaching units if ratios were higher than ¼

Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH· Hospital nurse staffing and patient mortality , nurse burnout, and job dissatisfaction. JAMA. 2002 Oct 23-30;288(16):1987-93

Table 3 – Use of specific analgesia for painful procedures by center

Center (n°)	Procedures carried out with specific preprocedural analgesia					
	All 5 painful procedures		Heel sticks		Vascular punctures	
	n/N*	%	n/N*	%	n/N*	%
1	89 / 1 356	6.6	3/ 8	37.5	35/ 67	52.2
2	162 / 4 091	4.0	22/ 926	2.4	114/ 207	55.1
3	1 614/ 3 239	49.8	939/ 1312	71.6	224/ 285	78.6
4	544 / 2 105	25.8	270/ 629	42.9	183/ 199	92.0
5	1 682 / 9 110	18.5	847/ 1 560	54.3	279/ 374	74.6
6	590/ 2 467	23.9	410/ 489	83.8	86/ 105	81.9
7	213 / 2 138	10.0	94/ 633	14.8	55/ 82	67.1
8	711 / 2 309	30.8	394/ 573	68.8	94/ 162	58.0
9	111 / 1 235	9.0	18/ 264	6.8	55/ 106	51.9
10	331 / 1 953	16.9	109/ 360	30.3	53/ 84	63.1
11	237 / 2316	10.2	140/ 643	21.8	43/ 75	57.3
12	200 / 983	20.3	87/ 241	36.1	37/ 60	61.7
13	1 240 / 4710	26.3	363/ 758	47.9	225/ 282	79.8
All centers	7 724/ 38 012	20.3	3 696/ 8 396	44.0	1 483/ 2088	71.0

*

Number of painful procedures performed with analgesia / total number of that specific procedure

Table 4. Differences in use of analgesia for procedures performed in the morning versus the rest of the day and for procedures performed in daytime versus nighttime.

	Number of procedures N	Procedures carried out with specific analgesia n %	Relative Reduction *	p *(chi2)*
MORNING VS REST OF THE DAY				
5 painful procedures				
Morning	9 861	2 546 25.8%		
Rest of the day	28 151	5 178 18.4%	28.8 %	**<0.001**
Heel sticks				
Morning	1 860	980 52.7%		
Rest of the day	6 536	2 716 41.6%	21.1 %	**<0.001**
Vascular punctures				
Morning	955	723 75.7%		
Rest of the day	1 133	760 67.1%	11.4 %	**<0.001**
DAYTIME VS NIGHTTIME				
5 painful procedures				
Daytime	19 059	4 261 22.5%		
Nighttime	18 953	3 463 18.3%	18.3 %	**<0.001**
Heel sticks				
Daytime	3 871	1 856 47.9%		
Nighttime	4 525	1 840 40.7%	15.2 %	**<0.001**
Vascular punctures				
Daytime	1 363	1 003 73.6%		
Nighttime	725	480 66.2%	10.0 %	**<0.001**

*Percentage of relative reduction in the use of specific analgesia

Table 5 - Interactions between differences in analgesia use during daytime and nighttime and characteristics of children, centers and procedures in univariate analysis

Factor		UNIVARIATE ANALYSIS						
		Procedures carried out with specific analgesia				Daytime compared to nighttime : Relative reduction[a]	Daytime compared to nighttime : OR	Interaction test (p)[b]
		Daytime		Nighttime				
		n/N	%	n/N	%			
Day of procedure[c]	D1	272/ 1 789	15.2	276/ 1 667	16.6	-8.9%	0.90 (0.75 -1.09)	
	D2-D14	3 989/17 164	23.2	3 187/17 392	18.3	21.2%	1.35 (1.28 -1.42)	**<10.3**
Mechanical ventilation	Yes	1 668/11 908	14.0	1 501/12 327	12.2	13.1%	1.18 (1.09 -1.27)	
	No	2 593/ 7 045	36.8	1 962/ 6 732	29.1	20.8%	1.42 (1.32 -1.52)	**<10-3**
Parental presence	Yes	331/ 1 488	22.2	131/ 485	27.0	-21.4%	0.77 (0.61 -0.98)	
	No	3 930/17 465	22.5	3 332/18 574	17.9	21.0%	1.33 (1.26 -1.40)	**<10-3**
Continuous analgesia	Yes	738/ 6 341	11.6	722/ 6 864	10.8	9.6 %	1.12 (1.01 -1.25)	
	No	3 523/12 612	27.9	2 741/12 195	22.5	19.5 %	1.34 (1.26 -1.42)	**0.005**
Surgery	Yes	337/ 1 576	21.4	300/ 1 714	17.5	18.2%	1.28 (1.08 -1.53)	
	No	3 924/17 377	22.6	3 163/17 345	18.2	19.5%	1.31 (1.24 -1.38)	0.829
Sex	Male	2 363/10 758	22.0	1 877/10 757	17.4	20.9%	1.33 (1.25 -1.43)	
	Female	1 898/ 8 198	23.2	1 586/ 8 302	19.1	17.6%	1.28 (1.18 -138)	0.410
Gestational age	≥ 37 weeks	583/ 3 803	15.3	435/ 3 796	11.5	25.2%	1.40 (1.22 -1.60)	
	< 37 weeks	3 678/15 150	24.3	3 028/15 263	19.8	18.3%	1.30 (1.23 -1.37)	0.295
Nurse shift	3 per day	1 634/ 5 995	27.3	1 276/ 5 907	21.6	20.7%	1.36 (1.25 -1.48)	
	2 per day	2 627/12 958	20.3	2 187/13 152	16.6	18.0%	1.28 (1.20 -1.36)	0.230
Nurse rotation	No	1 853/ 7 507	24.7	1 477/ 7 704	19.2	22.3%	1.38 (1.28 -1.49)	
	Yes	2 408/11 446	21.0	1 986/11 355	17.5	16.9%	1.26 (1.18 -1.34)	0.068
Pain coordinator	No	502/ 2 844	17.7	368/ 2 933	12.5	28.9%	1.49 (1.29 -1.73)	
	Yes	3 759/16 109	23.3	3 095/16 126	19.2	17.8%	1.28 (1.22 -1.35)	0.053
Written protocols for sucrose analgesia	Yes	3 663/15 325	23.9	3 155/15 508	20.3	14.9%	1.23 (1.17 -1.30)	
	No	598/ 3 628	16.5	308/ 3 551	8.7	47.4%	2.08 (1.80 -2.41)	**<10-3**
Parental presence authorized 24-hours	No	2 510/ 11 949	21.0	2 091/12 023	17.4	17.2%	1.26 (1.18 -1.35)	
	Yes	1 751/ 7 004	25.0	1 372/ 7 036	19.5	22.0%	1.28 (1.27 -1.49)	0.102
Night head nurse	No	2 843/12 348	23.0	2 399/12 889	18.6	19.2%	1.31 (1.23 -1.39)	
	Yes	1 418/ 6 605	21.5	1 064/ 6 170	17.2	19.7%	1.31 (1.20 -1.43)	0.955
Teaching status	Minor	1 798/ 7 222	24.9	1 511/ 7516	20.1	19.2%	1.32 (1.22 -1.42)	
	Major	2 463/11 731	21.0	1 952/11 543	16.9	19.5%	1.31 (1.22 -1.40)	0.864

[a] If positive, analgesia was higher during daytime [b] p value < 0.05 indicates that the factor modified the difference in analgesia use between daytime and nighttime in univariate

[c] related to admission

Table 6 – Significant interactions between differences in analgesia use during daytime and nighttime and characteristics of children, centers and procedures in a multivariate, multilevel analysis[a]

Factor	Interaction test (p-value)	Interaction direction		OR
		Increase difference[c]	Decrease difference[c]	
Day of procedure[b]	<0.001	D2-D14		1.55 (1.23-1.94)
Mechanical ventilation	<0.05	Absence of mechanical ventilation during procedure		1.21 (1.02-1.43)
Parental presence	<0.001		Parents present	0.59 (0.44-0.79)
Nurse shift	<0.01	12 hour nurse shifts		2.25 (1.23-4.12)
Written protocols for sucrose analgesia	<0.001	Absence of written protocols for sucrose analgesia		2.40 (1.74-3.30)

[a] This is a multilevel analysis. The exposure was time of procedure (daytime versus nighttime). Factors in level 1 (associated with procedure) were day of procedure, mechanical ventilation, parental presence and continuous analgesia. Factors in level 2 (associated with children) were surgery, sex and gestational age. Factors in level 3 (associated with center) were nurse shift, nurse rotation, pain coordinator, written protocols for sucrose analgesia, parental presence authorized 24-hours, night head nurse and teaching status). Interactions between each factor and daytime versus nighttime were included in the model. Only factors that significantly interacted with time of procedure are shown in the table.

[b] related to admission

[c] Refers to the difference in analgesia use during daytime compared to nighttime

Funding source and conflict of interest statement : This study was supported by grant funds from the Fondation CNP, and the Fondation de France, France. R Guedj received a grant from L'Académie de Médecine to work on this study. These funding agencies did not participate in any of the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. No financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work

Data Sharing : No available data sharing

Contributor's statement page

Romain Guedj : Dr Guedj analysed and interpreted the data. He drafted the initial manuscripted and approved the final manuscript as submitted.

Claude Danan : Dr Danan implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Patrick Daoud : Dr Daoud implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Véronique Zupan : Dr Zupan implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Sylvain Renolleau : Pr Renolleau implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Elodie Zana : Dr Zana implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Sophie Aizenfisz : Dr Aizenfisz implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Alexandre Lapillonne : Dr Lapillone implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Laure de Saint Blanquat : Dr de Saint Blanquat implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Michèle Granier : Dr Granier implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Philippe Durand : Dr Durand implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Florence Castela : Dr Castela implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Anne Coursol : Dr Coursol implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Philippe Hubert : Pr Hubert designed the study. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Patricia Cimerman : Mrs Cimerman designed the study. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Babak Khoshnood : Pr Khoshnood designed the study and interpreted the data. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

KJS Anand : Pr Anand designed the study. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Ricardo Carbajal : Pr Carbajal designed the study and interpreted the data. He reviewed and revised the manuscript, and he approved the final manuscript as submitted. He is guarantor

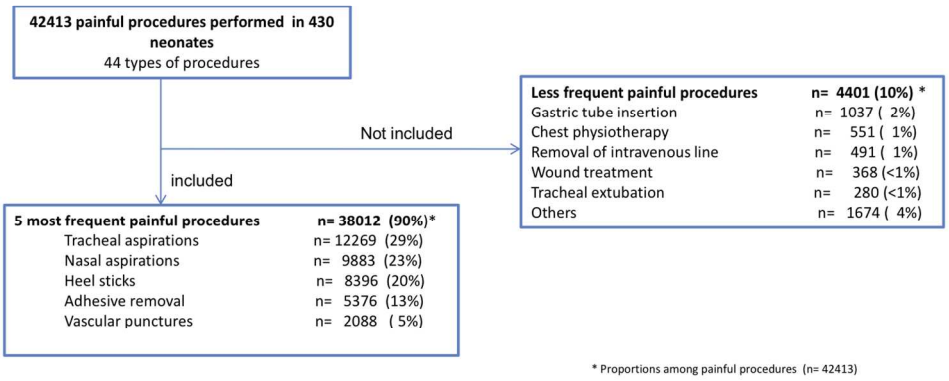


Figure 1 – Distribution of painful procedures analysed in the study

254x190mm (150 x 150 DPI)

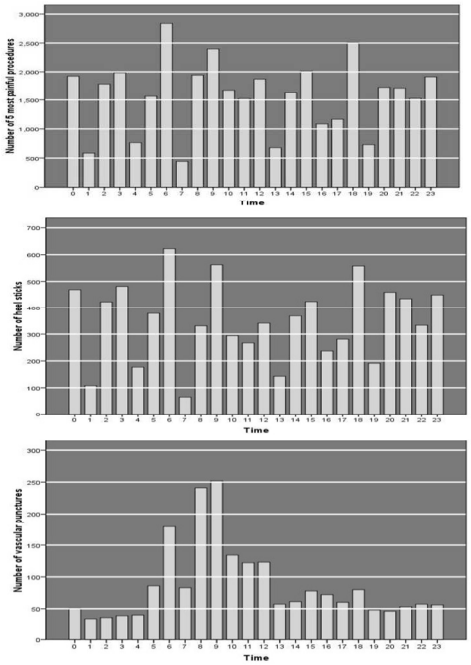


Figure 2 – Distribution of painful procedures by hour of the day
(Five most frequent painful procedures, n=38 012 ; Heel sticks, n = 8 396 ; Vascular punctures, n = 2 088)

254x190mm (150 x 150 DPI)

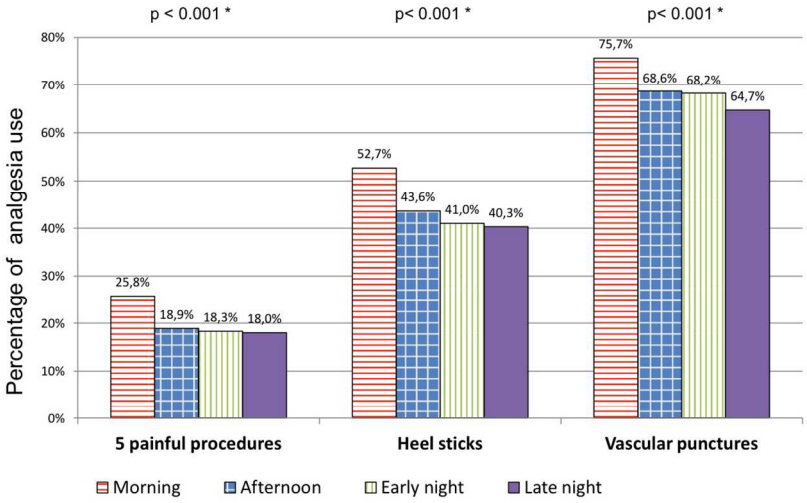


Figure 3 – Use of analgesia during each of the 6-hour period of the day for all procedures as well as for heel sticks and vascular punctures

*Global comparison of all four 6-hour periods
For all five painful procedures, heel sticks and vascular punctures, the comparison of morning vs each one of the other 6-hour periods was significant with p<0.001.
For heel sticks, the comparison of afternoon vs late night showed a p value = 0,032
All other pairwise comparisons were not significant

254x190mm (150 x 150 DPI)

Neonatal Pain Management is not the same During Days and Nights in Intensive Care Units: Analysis from the prospective EPIPPAIN Study

Strobe Checklist

TITLE AND ABSTRACT

1a/ (*a*) Indicate the study's design with a commonly used term in the title or the abstract
Done on page 1

***1b*) Provide in the abstract an informative and balanced summary of what was done and what was found**
Done

INTRODUCTION :

2/ Explain the scientific background and rationale for the investigation being reported
Done in paragraph 1 and 2 (page 2)

3/ State specific objectives, including any prespecified hypotheses
Done in paragraph 3

METHODS :

4/ Present key elements of study design early in the paper
Done in the first paragraph of the Methods section

5/ Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.
Setting and locations are described in the paragraph called "study center"
Period of recruitment is described in the paragraph called "study population".
Dates of exposure and data collection are described in the paragraph called "Data collection".

6/ Give the eligibility criteria, and the source and methods of selection of participants
This information is given in paragraphs called "study population" and "painful procedures"

7/ Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers.
The outcome (use of analgesia) is defined in paragraph named "painful procedures".
Exposures are defined in the paragraph named "data analysis".
Predictors and effect modifiers are presented in the "Data analysis" section and in the "Clinical factors associated with diurnal variations in analgesia"

8/ For each variable of interest, give sources of data and details of methods of assessment.
All patient and procedure variables were collected prospectively and systematically. Center variables were collected retrospectively. This information is stated in the Methods section.

9/ Describe any efforts to address potential sources of bias.
We motivated all staff from all participating centers to obtain a 100% inclusion rate so that data reflect real practices.

10/ Explain how the study size was arrived at
A 6-week data collection period for each unit was considered sufficient to study the practices of all rotating personnel and to minimize temporal changes in clinical practices. This is stated in the Method section.

11/ Explain how quantitative variables were handled in the analyses.
Quantitative variables existed only in demographic data and these were described as mean (SD) and median (interquartile range). There were no other quantitative variables.

12/ a Describe all statistical methods, including those used to control for confounding
These methods are included in paragraph named "data analysis"

12b/ Describe any methods used to examine subgroups and interactions
These methods are included in paragraph named "data analysis"

12c/ Explain how missing data were addressed
There were no missing data.

RESULTS

13a/ Report numbers of individual at each stage of study,
b/ Give reasons for non-participation at each stage
c/ Consider use of a flow diagram
This information is given in paragraphs called "painful procedures" of methods section and in figure 1.

14a/ Give characteristics of study population and information on exposures and potential confounders
b/ Indicate number of participants with missing data for each variable of interest
This information is given in tables 1, 2 and 3 and in the first paragraph of results section.

15/ Reports number of outcome events
This information is given in paragraph named "specific analgesia treatment"

16a/ Give unadjusted estimates and if applicable, confounder-adjusted estimates and their precision. Make clear which confounders were adjusted for and why they were included.
Unadjusted estimates are given in table 4.
Confounder-adjusted estimates are given in paragraph named “clinical factors associated with diurnal variation in analgesia”.
16b and c : not applicable

17/ Report other analyses done
Analyses of interactions are reported in table 5 and 6

DISCUSSION

18/ Summarise key results with reference to study objectives
Key results are summarized in the first two paragraphs.

19/ Discuss limitations of the study, taking into account sources of bias or imprecision.
Limitations are discussed in the last paragraph.

20/ Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Done

21/ Discuss the generalisability of the study results
Generalisabilty is discussed in paragraph 3.

OTHER INFORMATION

22/ Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.
The funding agencies of the Epippain study are listed in the manuscript.

Neonatal Pain Management is not the same During Days and Nights in Intensive Care Units

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004086.R1
Article Type:	Research
Date Submitted by the Author:	03-Dec-2013
Complete List of Authors:	Guedj, Romain; AP-HP - Hôpital Armand Trousseau, Service d'urgences pédiatriques; Inserm U-953, Danan, Claude; Centre Hospitalier Intercommunal de Creteil, Unité de réanimation néonatale Daoud, Patrick; Centre Hospitalier André Grégoire, Réanimation Infantile Zupan, Véronique; AP-HP, Hôpital ANtoine Béclère, Pédiatrie et Réanimation néonatale Renolleau, Sylvain; AP-HP, Hôpital Armand Trousseau, Réanimation Néonatale et Pédiatrique Zana-Taieb, Elodie; Médecine néonatale Port-Royal-Cochin, NICU Aizenfisz, Sophie; AP-HP, Hôpital Robert Debré, Réanimation pédiatrique Lapillonne, Alexandre; Université Paris descartes, AP-HP, Hôpital Necker-Enfants Malades, Réanimation néonatale de Saint Blanquat, Laure; Hôpital Necker, PICU Granier, Michele; Hôpital sud-francilien, NICU Durand, Philippe; Bicetre Hospital, Paediatric Intensive Care Unit Castela, Florence; Hôpital Poissy, Unité de réanimation néonatale Coursol, Anne; CH René Dubos, NICU Hubert, Philippe; Hopital Necker Paris, intensive care unit Cimerman, Patricia; Hopital Armand Trousseau, Centre National de Ressources de lutte contre la Douleur Anand, Sunny; Le Bonheur Children's Hospital, University of Tennessee Health Science Center Khoshnood, Babak; Hopital Saint Vincent de Paul, INSERM U953 Carbajal, Ricardo; Hôpital Trousseau, Service des Urgences Pédiatriques
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Intensive care
Keywords:	NEONATOLOGY, after hour care, painful procedures, Pain

Neonatal Pain Management is not the same During Days and Nights in Intensive Care Units

Authors : Romain Guedj[1], MD, Claude Danan[2], MD, Patrick Daoud[3], MD, Véronique Zupan[4], MD, Sylvain Renolleau[5], MD, PhD, Elodie Zana[6], MD, Sophie Aizenfisz[7], MD, Alexandre Lapillonne[8], MD, PhD, Laure de Saint Blanquat[9], MD, Michèle Granier[10], MD, Philippe Durand[11], MD, Florence Castela[12], MD, Anne Coursol[13], MD, Philippe Hubert[14], MD, PhD, Patricia Cimerman[15], Research Nurse, Babak Khoshnood[16], PhD, KJS Anand[17], MD, PhD, Ricardo Carbajal[18], MD, PhD.

[1] Inserm U-953, 75020 Paris ; AP-HP, Hôpital Armand-Trousseau, Service d'urgences pédiatriques, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

M.D.

[2] Centre Hospitalier Intercommunal de Créteil, Unité de réanimation néonatale et soins intensifs, 40 avenue de Verdun 94010 Créteil Cedex, France

M.D.

[3] Centre HospitaIier André Grégoire, Réanimation infantile, 56, bd de la Boissiere 93105 Montreuil-sous-Bois Cedex, France

M.D.

[4] AP-HP, Hôpital Antoine Béclère, Pédiatrie et Réanimation Néonatale, 157, rue de la Porte de Trivaux 92141 Clamart cedex, France

M.D.

[5] AP-HP, Hôpital Armand-Trousseau, Réanimation Néonatale et Pédiatrique, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

PhD

[6] Maternité Port-Royal, Réanimation néonatale, 123 boulevard Port Royal, 75014 Paris, France

M.D.

[7] AP-HP, Hôpital Robert Debré, Réanimation et Surveillance continue pédiatrique, 48 boulevard sérurier 75019 Paris, France

M.D.

[8] Université Paris Descartes, AP-HP, Hôpital Necker-Enfants Malades, Réanimation Néonatale, 149 rue de Sèvres 75015 Paris, France

Ph.D

[9] AP-HP, Hôpital Necker-Enfants Malades, Réanimation Polyvalent Pédiatrique, 7149 rue de Sèvres, 75015 Paris, France

M.D.

[10] Centre Hospitalier Sud Francilien, Médecine Néonatale, 116 boulevard Jean Jaurès, 91100 Corbeil, France

M.D.

[11] AP-HP, Hôpital Bicêtre, Réanimation Néonatale et Pédiatrique, 78 rue du général Leclerc, 94275 Kremlin-Bicêtre, France

M.D.

[12] Centre Hospitalier Intercommunal, Hôpital Poissy, Unité de Réanimation Néonatale, 23 boulevard Gambetta, 78100 Poissy, France

M.D.

[13] Centre Hospitalier René Dubos, Médecine Néonatale et Réanimation Pédiatrique, 6 avenue de l'Ile de France, 95303 Pontoise, France

M.D.

[14] AP-HP, Hôpital Necker-Enfants Malades, Réanimation Polyvalent Pédiatrique, 149 rue de Sèvres, 75015 Paris, France

PhD

[15] AP-HP, Hôpital Armand-Trousseau, Centre Nationale de Ressources de lutte contre la Douleur26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

RN (Research nurse)

[16] Inserm U953, Maternité Port-Royal, , 123 boulevard Port Royal, 75014 Paris, France

PhD

[17] University of Tennessee Health Science Center & Le Bonheur Children's Hospital, Memphis, TN

PhD

[18] Inserm U-953, 75020 Paris ; AP-HP, Hôpital Armand-Trousseau, Service d'urgences pédiatriques, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France; Université Pierre et Marie Curie, 75006 Paris

PhD

Corresponding author : Romain GUEDJ, Service des urgences pédiatriques, Hôpital Trousseau, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12

Phone: + 33 144 736 487 Fax: +33 144 736 985

Email : romainguedj@gmail.com

Abbrévations :

NICU : Neonatal intensive care unit

OR : Odd ratio

PICU : Pediatric intensive care unit

Key words :

Pain ; Neonate ; Neonatology and infant care ; After-hours care ; painful procedures ; pain

Word count : 2 717 words.

Abstract

Objective : To determine whether analgesic use for painful procedures performed in neonates in the Neonatal intensive care unit (NICU) differs during nights and days and during each of the 6-hour period of the day.

Design : Conducted as part of the prospective observational EPIPPAIN study which was designed to collect in real time and around-the-clock bedside data on all painful or stressful procedures

Setting : 13 NICUs and PICUs in the Paris Region, France.

Participants: All 430 neonates admitted to the participating units during a 6-week period between September 2005 and January 2006.

Data collection. During the first 14 days of admission data were collected on all painful procedures and analgesic therapy. The five most frequent procedures representing 38012 of all 42413 (90%) painful procedures were analyzed.

Intervention : Observationnal study

Main outcome assesment : We compared the use of specific analgesia for procedures performed during each of the 6-hour periods of a day: Morning (7:00AM to 12:59PM), Afternoon, Early Night and Late Night, and during Daytime (Morning+Afternoon) and Nighttime (Early Night+Late Night).

Results: 7724 out of 38012 (20.3%) painful procedures were carried out with a specific analgesic treatment. For Morning, Afternoon, Early Night and Late night, respectively, the use of analgesia was 25.8%, 18.9%, 18.3% and 18%. The relative reduction of analgesia was 18.3%, $p<0.01$, between Daytime and Nighttime and 28.8%, $p<0.001$, between Morning and the Rest of the day. Parental presence, nurse 8-hour shifts and written protocols for analgesia were associated with a decrease in this difference.

Conclusion : The substantial differences in the use of analgesia around-the clock may be questioned on quality of care grounds.

Article summary :

Article focus : Some epidemiological studies focused on mortality-risk and medical errors raise concern about the homogeneity of care around the clock. Variation of analgesic use for painful procedure in neonates in intensive care units during day has never been studied.

Key messages : Specific analgesia for paiful procedures was more frequent during daytime than nighttime. It gradually decreased from morning to late night. Pain management guidelines should include standardization of care across 24 hours.

Main strenghts and limitations of this study : This is the first prospective multicenter study to show variations in analgesic practices around-the clock. The around the clock variations in analgesia use for procedural pain management did not correspond to an isolated practice of a single center but rather to the practices of a large geographical region.

Patients and their families expect that the same quality of care be provided to patients 24 hour-a-day. In reality, some epidemiological studies, mainly focused on mortality-risk and medical errors have found poorer outcomes for hospital care given during evening or night-time hours.[1–7] Among neonates, one study reported that perinatal mortality rates fluctuated according to the hour of birth with a peak occurring in the evening[3] and another study found a higher mortality for term neonates born in the evenings, nights or weekends.[4] These studies raise concern about the homogeneity of care in settings where patients expect safe and high quality care 24 hour-a-day. Significant practice variability also occurs in many other aspects of care. To our knowledge, the variation of neonatal pain management during day and night shifts has not been studied yet.

Neonatal pain management has received much attention during the last two decades leading professional societies to issue guidelines to improve pain management in this vulnerable population.[8,9]. These guidelines highlight the necessity to improve analgesia for invasive procedures, which constitute the main source of pain in sick or premature infants admitted to the neonatal intensive care unit (NICU). However, surveys of clinical practices suggest that many evidence-based interventions have not been applied effectively in NICUs[10] and that wide gaps exist between knowledge and practice.[11] The undertreatment of pain in this population would be aggravated by variations in analgesic use according to the time of the day. Thus, the question about variation of quality of pain management during day and night is of practical relevance.

We designed this study to determine whether analgesic use for painful procedures performed in neonates in the NICU and the Pediatric intensive care unit (PICU) differs during nights and days and during four 6-hour periods of the day. This study was conducted as part of the EPIPPAIN study.[12]

METHODS

Study centers

The detailed methodology of the EPIPPAIN study was published elsewhere.[12] EPIPPAIN was a prospective observational study designed to collect 24-hours a day bedside data on all painful or stressful procedures performed in neonates admitted to NICUs and PICUs of a geographically defined region. All 14 tertiary care centers, NICUs and PICUs in the Paris Region were invited to participate and 13 accepted the invitation.

All the participating units had developed their pain management protocols locally. No instructions were given to modify the standard of care for procedural pain management in neonates. The study protocol and the data collection forms were reviewed by the local committee for the protection of human subjects.

Study population

We included in this study all neonates admitted to the participating units during a 6-week period between September 2005 and January 2006. Inclusion criterion was admitted preterm neonates younger than 45 postconceptional weeks and term neonates younger than 28 days. There were no exclusion criteria.

Data collection

During the first 14 days of admission to the participating units, prospective data were collected on all neonatal procedures causing pain, stress, or discomfort with the corresponding analgesic therapy. Specific pre-procedural analgesia included nonpharmacological (eg, sweet solutions, sucking) or pharmacological treatments (eg, single- or multiple drug doses). Nursing and medical staff at the bedside recorded all procedures on a specific form in real

time. Since the EPIPPAIN study did not include data about the characteristics of the participating units, we conducted in March 2010 a phone survey with each head nurse present at the time of the initial study (2005-2006). We inquired about nurse shifts (two or three per day), shift rotation (between day and night), existence of a pain coordinator, written standardized protocols for sucrose analgesia, parental presence authorized 24-hours a day, ratios of residents to number of beds in order to describe the teaching status,[13] and existence of a night head nurse.

Painful procedures

The EPIPPAIN study collected data on 430 neonates who underwent 60969 procedures. Because the current international definition of pain[14] does not apply to neonates, we chose a published empirical approach to define pain. This describes pain as an inherent quality of life that appears early in ontogeny to serve as a signaling system for tissue damage.[15] Thus, a procedure was considered painful if it invaded the neonate's bodily integrity, causing skin injury or mucosal injury from the introduction or removal of foreign material into airway or digestive or urinary tract. Of these 60969 procedures, 42413 were considered painful, including 44 different procedures. In order to study the differences in analgesic management during the 24 hours of the day, we selected the five most frequent procedures that would both be readily performed at any time in an intensive care unit and also represent the majority of painful procedures : nasal or tracheal suctioning, heel sticks, adhesive removals, and vascular punctures (arterial punctures, venipunctures and intravenous cannulas). As shown in figure 1, these five procedures accounted for 90% of all painful procedures.

The use of procedural analgesia was defined as the use of specific analgesia given prior to painful procedures (pharmacological or nonpharmacological therapy).

Data analysis

Data were double entered into a relational database (EpiData Entry, version 3·0, Odense, Denmark) and analyzed with SPSS, v14 for Windows, (SPSS Inc, Chicago, Illinois) and Stata v.10.0 software (Stata Corporation, College Station, TX, USA). Procedures were distributed according to the time when they were performed, into four 6-hour periods: Morning (from 7:00AM to 12:59PM), Afternoon (from 1:00PM to 6:59PM), Early Night (from 7:00PM to 0:59AM) and Late Night (from 1:00AM to 6:59AM). We also defined Daytime as Morning + Afternoon and Nighttime as Early Night + Late Night. These timings were chosen because in France most of the day and night nurse shifts start at 7:00am and 7:00pm, respectively. Descriptive statistics were used to summarize continuous and categorical variables.

The outcome was the use of procedural analgesia. We calculated the percentage of use of procedural analgesia for each of the 6-hour periods, Daytime, Nighttime and for the period including Afternoon + Early Night + Late Night. Since data were not independent, procedures were clustered by child and center. Therefore, the use of procedural analgesia was compared across periods using a multilevel model with random effect at child and center levels.

We assessed changes in the effect of time of day across center by computing specific center crude OR to test heterogeneity of the ORs across centers. Then, we constructed a model including procedures and children characteristics that were found to be associated with the use of specific analgesia prior to procedures in the EPIPPAIN study (Day of procedure, mechanical ventilation, parental presence, continuous analgesia, surgery, sex, and gestational age) and variables describing centers (nurse shift, nurse rotation, pain coordinator, written protocols for sucrose analgesia, policy on parental presence authorized 24-hours, night head nurse and teaching status). In order to investigate factors associated with differences in analgesia use 24-hours a day, we tested the interactions between analgesia use and the characteristics of newborns, centers, and procedures.. We used a multilevel logistic regression model with random intercept and random slope in order to test cross level interactions and to

control for confounding factors.[16,17] In this multilevel analysis, procedure, child and center were at the lowest, second and highest level, respectively.

All the described factors were included in our model and all interactions between time of procedures (daytime or nighttime) and each covariate were obtained. Results are presented as point estimate odds ratios (ORs) with 2-sided 95% confidence intervals (CI). The threshold for statistical significance was set up at a probability value of <0.05.

RESULTS

From the 430 neonates included in the study, 309 (71.9%) were from NICUs and 121 (28.1%) from PICUs. The mean (SD) length of stay was 8.4 (4.6) calendar days and the observation period represented 3598 patient-days. The overall rate of mechanical tracheal ventilation was 70.5%, but it varied from 46.2% to 92% across units. Table 1 lists the demographic characteristics of the study population and Table 2 lists the characteristics of the participating centers. Appendix 1 shows the distribution of painful procedures by hour of the day. Overall, 7724 out of 38012 (20.3%) painful procedures were carried out with the provision of a specific analgesic treatment. Regarding heel sticks and vascular punctures, 3696/8396 (44.0%) and 1483/2088 (71.0%), respectively, were performed with specific analgesia..

Analgesia use according to time of the day

For Morning, Afternoon, Early Night and Late Night, respctively, the use of analgesia was 25.8%, 18.9%, 18.3% and 18% (p< 0.001). Figure 2 shows the use of analgesia for each 6-hour period of the day by category of procedures. For all painful procedures taken together or for skin-breaking procedures, the use of analgesia was higher in the morning, decreased during the day and was lowest in the late night.

For all procedures taken together or for skin breaking procedures analyzed separately, the use of analgesia was significantly higher for procedures performed in the morning versus the rest of the day, ($p<0.001$ for all painful procedures, $p<0.01$ for heel sticks and vascular punctures), as well as for all painful procedures ($p<0.01$) and heel sticks ($p<0.05$) performed during the daytime versus the nighttime, Use of analgesia was close to be significantly higher for vascular punctures performed during daytime versus nightime ($p = 0.07$). Table 3.

Factors associated with Diurnal Variations in Analgesia

Use of analgesia varied widely among centers (from 4.0% to 49.8%) as shown in appendix 2. Moreover, difference of use analgesia between daytime and nighttime significantly varied among centers as shown in figure 3.

Interactions between differences in analgesia use during daytime and nighttime and the characteristics of children, centers and procedures in univariate analysis are listed in Table 4. We can see for instance that regarding mechanical ventilation the relative reduction in analgesia use during nighttime compared to daytime was 13.1% in invasively ventilated infants and 20.8% in spontaneously breathing or non-invasively ventilated infants.

The inclusion of all clinical factors in a multilevel analysis, showed that analgesia use was significantly higher for procedures performed during the daytime versus the nighttime, (OR = 2.25 [1.10–4.60], $p< 0.05$). In this multilevel model, day of procedure (related to admission), mechanical ventilation, parental presence, nurse shift, and written protocol for analgesia significantly interacted with time of procedure, as shown in table 5. (the whole list of ORs from the model is shown in appendix 3). Presence of parents reversed the difference of use of analgesia between daytime and nighttime; i.e. analgesia was significantly more frequent in nighttime than in daytime when parents were presents.

DISCUSSION

This is the first prospective multicenter study to show variations in analgesic practices around-the clock. The use of specific analgesia for painful procedures was more frequent during daytime than nighttime. Moreover, we found a sharp decrease in use of analgesia from morning to afternoon followed by a gentle decline thereafter.

The relative reduction in the use of specific analgesia between daytime and nighttime was 18.3% for all five painful procedures and this difference reached 28.8% between the morning and the rest of the day. Such substantial differences in the use of analgesia may be questioned on quality of care grounds. We consider that the lower use of analgesia during those periods represents a marker of poor quality care that needs to be overcome. The differences in analgesia use between daytime and nighttime that we found in this study were independent of the type of procedure and whether the procedure was more frequently performed during a period of the day. In fact, heel sticks were homogeneously distributed around-the clock and vascular punctures were more frequent during the morning, but the differences in analgesia use were very similar and consistent (Appendix 1).

The around the clock variations in analgesia use for procedural pain management did not correspond to an isolated practice of a single center but rather to the practices of a large geographical region. The participation of all but one center in this region, the uniform data collection at all centers, and 100% patient inclusion during the study period ensure that the study cohort was representative of NICU procedural pain management in the Paris region. The extrapolation of these results to the entire French territory may be possible but not totally certain because of conflincting arguments. On one side, (i) the Paris region is the most populated region in France and practices within this area closely may reflect those of the country and (ii) analgesia use was significantly more frequent during daytime than nighttime

in eight of thirteen centers but on the other side, the analysis of crude OR by center did not show homogeneity (figure 3).

The variation of quality of neonatal care over the day has been rarely studied directly. Most studies have used outcomes as a proxy to assess this variation. Some studies reported increased rates of perinatal death at night.[3–5] Although mortality could be considered as an important proxy to assess quality of care, it has the disadvantage of being related to only serious or critical conditions and it is exposed to several confounding factors. Medication error rate has also been used in a few studies to assess variations in quality of care. It has been found that errors were higher during nighttime than during daytime.[6, 20] However, care quality cannot be restricted to a safety problem. Optimal care quality implies, among other standards, care without pain. Thus, analgesic use for painful procedure is also a parameter to measure care quality.

In an attempt to explain our findings, we investigated factors associated with differences of analgesia use around-the-clock. Parental presence, nurse 8-hour shifts and written protocols for analgesia decreased the difference of analgesia use between day and night. These results suggest that written protocols or parental presence may limit the reduction of analgesia use during nighttime. Protocols limit the freedom of health care providers about the management of pain, making the practice of caregivers more homogeneous. It has been reported that the presence of protocols, by harmonizing practices, increases the quality of care.[10] Similarly, it has been reported that the presence of parents influences the practice of caregivers.[18] Our data also suggest that shorter hour shifts (8-hour) for nurses decrease the difference of analgesia use between day and night. In other health care areas, it has been shown that 12-hours shifts negatively influence the behavior of care providers yielding to less efficient

care.[19,20] However, the area of variations in pain management practices is highly complex and to attempt to explain it by staffing or protocols is probably simplistic. Other factors that we have not studied could play a role. Contextual factors may influence staff behaviors. Although number of nurses is homogeneous during daytime and nighttime in French NICUs, more medical staff is around in the morning and in the afternoon. Interprofessional collaboration practices[21] and higher access to personnel to care for complex patients[22] may enhance pain practices. Thus, analgesic use may also be influenced by the total number of staff and not only nurses.

We acknowledge two limitations of this study. First, a potential bias would be a difference in quality of data collection during days and nights. We consider that this is not likely because we ensured a completeness of reporting by verifying from the patients' charts that all procedures were documented on the study datasheets. Furthermore, there is no reason that a nurse recorded a procedure but not the use of analgelsia. Second, we collected data about the characteristics and organization of center in a retrospective manner 5 years after the collection of clinical data. This might have introduced a bias. However, we feel that this bias was minimized because we obtained data from the head nurse who usually keeps records of all organizational details. Since we only had 13 centers, data about organizational characteristics should be looked upon with caution.

CONCLUSION

Our findings suggest that the constant efforts to improve care quality should also include standardization of care across 24 hours and pain management guidelines should reinforce this message. The variation of care quality during the day is certainly a complex phenomenon that deserves further research. It appears that human factors intervene in the process of care delivery and we need to better understand them in order to improve care quality. Our results suggest that the modification of organisational factors such as parental presence and written protocols may contribute to the homogenization of quality of care around the clock.

Aknowledgment

We would like to aknowledge l'Académie de Médecine

Funding and Competing Interests

This study was supported by grant funds from the Fondation CNP, and the Fondation de France, France. R Guedj received a grant from L'Académie de Médecine to work on this study. These funding agencies did not participate in any of the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. No financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work

Contributorship Statement

Romain Guedj: Dr Guedj participated in the design of study hypothesis, analysed and interpreted the data. He drafted the initial manuscripted and approved the final manuscript as submitted.

Claude Danan: Dr Danan implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Patrick Daoud: Dr Daoud implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Véronique Zupan: Dr Zupan implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Sylvain Renolleau: Pr Renolleau implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Elodie Zana: Dr Zana implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Sophie Aizenfisz: Dr Aizenfisz implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Alexandre Lapillonne: Dr Lapillone implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Laure de Saint Blanquat: Dr de Saint Blanquat implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Michèle Granier: Dr Granier implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Philippe Durand: Dr Durand implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Florence Castela: Dr Castela implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Anne Coursol : Dr Coursol implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Philippe Hubert: Pr Hubert participated in the design of the study. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Patricia Cimerman Mrs Cimerman participated in the design of the study. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Babak Khoshnood: Pr Khoshnood participated in the design of the study and interpreted the data. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

KJS Anand: Pr Anand participated in the design of the study. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Ricardo Carbajal : Pr Carbajal designed the study and interpreted the data. He reviewed and revised the manuscript, and he approved the final manuscript as submitted. He is the guarantor of this study

Data Sharing Statement

No available data sharing

REFERENCES

1. Duke GJ, Green JV, Briedis JH. Night-shift discharge from intensive care unit increases the mortality-risk of ICU survivors. Anaesth Intensive Care. oct 2004;32(5):697□701.

2. Laupland KB, Shahpori R, Kirkpatrick AW, et al.Hospital mortality among adults admitted to and discharged from intensive care on weekends and evenings. J Crit Care. sept 2008;23(3):317□324.

3. Paccaud F, Martin-Béran B, Gutzwiller F. Hour of birth as a prognostic factor for perinatal death. Lancet. 13 févr 1988;1(8581):340□343.

4. Pasupathy D, Wood AM, Pell JP, et al.Time of birth and risk of neonatal death at term: retrospective cohort study. BMJ. 2010;341:c3498.

5. Stephansson O, Dickman PW, Johansson ALV, et al.Time of birth and risk of intrapartum and early neonatal death. Epidemiology. mars 2003;14(2):218□222.

6. Miller AD, Piro CC, Rudisill CN, et al. Nighttime and weekend medication error rates in an inpatient pediatric population. Ann Pharmacother. nov 2010;44(11):1739□1746.

7. Hendey GW, Barth BE, Soliz T. Overnight and Postcall Errors in Medication Orders. Academic Emergency Medicine. 1 juill 2005;12(7):629□634.

8. Anand KJ. Consensus statement for the prevention and management of pain in the newborn. Arch Pediatr Adolesc Med. févr 2001;155(2):173□180.

9. Prevention and management of pain and stress in the neonate. American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee. Pediatrics. févr 2000;105(2):454□461.

10. Sharek PJ, Powers R, Koehn A, et al. Evaluation and development of potentially better practices to improve pain management of neonates. Pediatrics. nov 2006;118 Suppl 2:S78□86.

11. Spence K, Henderson-Smart D. Closing the evidence-practice gap for newborn pain using clinical networks. J Paediatr Child Health. mars 2011;47(3):92□98.

12. Carbajal R, Rousset A, Danan C, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. JAMA. 2 juill 2008;300(1):60□70.

13. Aiken LH, Clarke SP, Sloane DM, et al. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. JAMA. 23 oct 2002;288(16):1987□1993.

14. Pain terms: a list with definitions and notes on usage. Recommended by the IASP

Subcommittee on Taxonomy. Pain. juin 1979;6(3):249.

15. Anand KJ, Craig KD. New perspectives on the definition of pain. Pain. sept 1996;67(1):3□6; discussion 209□211.

16. Merlo J, Chaix B, Ohlsson H, et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. J Epidemiol Community Health. avr 2006;60(4):290□297.

17. Merlo J, Chaix B, Yang M, et al. A brief conceptual tutorial on multilevel analysis in social epidemiology: interpreting neighbourhood differences and the effect of neighbourhood characteristics on individual health. J Epidemiol Community Health. déc 2005;59(12):1022□1028.

18. Johnston C, Barrington KJ, Taddio A, et al. Pain in Canadian NICUs: have we improved over the past 12 years? Clin J Pain. avr 2011;27(3):225□232.

19. Borges FN da S, Fischer FM. Twelve-hour night shifts of healthcare workers: a risk to the patients? Chronobiol Int. mars 2003;20(2):351□360.

20. Macias DJ, Hafner J 2nd, Brillman JC, et al. Effect of time of day and duration into shift on hazardous exposures to biological fluids. Acad Emerg Med. juin 1996;3(6):605□610.

21. Latimer MA, Johnston CC, Ritchie JA, et al. Factors affecting delivery of evidence-based procedural pain care in hospitalized neonates. J Obstet Gynecol Neonatal Nurs. avr 2009;38(2):182□194.

22. Stevens B, Riahi S, Cardoso R, et al. The influence of context on pain practices in the NICU: perceptions of health care professionals. Qual Health Res. juin 2011;21(6):757□770.

Table 1. Demographic characteristics of 430 neonates

Characteristics	Number (%)	Mean (SD)	Median (IQR)	Range
Gestational age group at birth 24-29 wk 30-32 wk 33-36 wk 37-42 wk	 119 (27.7) 108 (25.1) 84 (19.5) 119 (27.7)			
Birth weight (g)		1962 (957)	1743 (1155-2738)	490-4760
Male	237 (55.1)			
Inborn (born at study hospital)	237 (55.1)			
Age at admission (h)			2.5 (0.5 – 24.0)	
Surgery during the study period	30 (7.0)			
Mechanical tracheal ventilation	303 (70.5)			
Duration of participation (d) Overall 24-29 wk 30-32 wk 33-36 wk 37-42 wk	 	 8.4 (4.6) 11.6 (3.8) 8.7 (4.6) 6.6 (4.0) 6.0 (3.9)	 8.0 (4.0-14.0) 14.0 (9.0-14.0) 9.0 (4.0-14.0) 6.0 (3.0-9.0) 5.0 (3.0-8.0)	 1-14 2-14 1-14 2-14 1-14
Hospitalized for more than 14 days	126 (29.3)			
Died during the study period	24(5.6)			

Table 2: Characteristics of centers

	Number of centers n = 13
Nurse shift	
2 per day	9
3 per day	4
Day-night nurse rotation	
Yes	7
No	6
Pain coordinator	
Yes	10
No	3
Written standardized protocols for sucrose analgesia	
Yes	11
No	2
Parental presence authorized 24-hours	
Yes	6
No	7
Teaching status*	
Minor	6
Major	7
Night head nurse	
Yes	2
No	11

* postgraduate trainees /bed ratio : minor teaching units if ratios were ¼ or less, major teaching units if ratios were higher than ¼

Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH· Hospital nurse staffing and patient mortality , nurse burnout, and job dissatisfaction. JAMA. 2002 Oct 23-30;288(16):1987-93

Table 3. Differences in use of analgesia for procedures performed in the morning versus the rest of the day and for procedures performed in daytime versus nighttime.

	Number of procedures N	Procedures carried out with specific analgesia n %	Relative Reduction *	Univariate analysis p
MORNING VS REST OF THE DAY				
5 painful procedures				
Morning	9 861	2 546 25.8%		
Rest of the day	28 151	5 178 18.4%	28.8 %	**<0.001**
Heel sticks				
Morning	1 860	980 52.7%		
Rest of the day	6 536	2 716 41.6%	21.1 %	**<0.01**
Vascular punctures				
Morning	955	723 75.7%		
Rest of the day	1 133	760 67.1%	11.4 %	**<0.01**
DAYTIME VS NIGHTTIME				
5 painful procedures				
Daytime	19 059	4 261 22.5%		
Nighttime	18 953	3 463 18.3%	18.3 %	**<0.01**
Heel sticks				
Daytime	3 871	1 856 47.9%		
Nighttime	4 525	1 840 40.7%	15.2 %	**<0.05**
Vascular punctures				
Daytime	1 363	1 003 73.6%		
Nighttime	725	480 66.2%	10.0 %	**0.07**

*Percentage of relative reduction in the use of specific analgesia

**These are results from multilevel analysis with time of day as the only explanatory variable. In this multilevel analyses, procedure, child and center were at the lowest, second and highest level, respectively.

Table 4 - Interactions between differences in analgesia use during daytime and nighttime and characteristics of children, centers and procedures in univariate analysis

Factor		UNIVARIATE ANALYSIS						
		Procedures carried out with specific analgesia				Daytime compared to nightime : Relative reduction[a]	Daytime compared to nightime : OR	Interaction test (p)[b]
		Daytime		Nightime				
		n/N	%	n/N	%			
Day of procedure[c]	D1	272/ 1 789	15.2	276/ 1 667	16.6	-8.9%	0.90 (0.75 -1.09)	
	D2-D14	3 989/17 164	23.2	3 187/17 392	18.3	21.2%	1.35 (1.28 -1.42)	**<10.3**
Mechanical ventilation	Yes	1 668/11 908	14.0	1 501/12 327	12.2	13.1%	1.18 (1.09 -1.27)	
	No	2 593/ 7 045	36.8	1 962/ 6 732	29.1	20.8%	1.42 (1.32 -1.52)	**<10-3**
Parental presence	Yes	331/ 1 488	22.2	131/ 485	27.0	-21.4%	0.77 (0.61 -0.98)	
	No	3 930/17 465	22.5	3 332/18 574	17.9	21.0%	1.33 (1.26 -1.40)	**<10-3**
Continuous analgesia	Yes	738/ 6 341	11.6	722/ 6 864	10.8	9.6 %	1.12 (1.01 -1.25)	
	No	3 523/12 612	27.9	2 741/12 195	22.5	19.5 %	1.34 (1.26 -1.42)	**0.005**
Surgery	Yes	337/ 1 576	21.4	300/ 1 714	17.5	18.2%	1.28 (1.08 -1.53)	
	No	3 924/17 377	22.6	3 163/17 345	18.2	19.5%	1.31 (1.24 -1.38)	0.829
Sex	Male	2 363/10 758	22.0	1 877/10 757	17.4	20.9%	1.33 (1.25 -1.43)	
	Female	1 898/ 8 198	23.2	1 586/ 8 302	19.1	17.6%	1.28 (1.18 -138)	0.410
Gestational age	≥ 37 weeks	583/ 3 803	15.3	435/ 3 796	11.5	25.2%	1.40 (1.22 -1.60)	
	< 37 weeks	3 678/15 150	24.3	3 028/15 263	19.8	18.3%	1.30 (1.23 -1.37)	0.295
Nurse shift	3 per day	1 634/ 5 995	27.3	1 276/ 5 907	21.6	20.7%	1.36 (1.25 -1.48)	
	2 per day	2 627/12 958	20.3	2 187/13 152	16.6	18.0%	1.28 (1.20 -1.36)	0.230
Nurse rotation	No	1 853/ 7 507	24.7	1 477/ 7 704	19.2	22.3%	1.38 (1.28 -1.49)	
	Yes	2 408/11 446	21.0	1 986/11 355	17.5	16.9%	1.26 (1.18 -1.34)	0.068
Pain coordinator	No	502/ 2 844	17.7	368/ 2 933	12.5	28.9%	1.49 (1.29 -1.73)	
	Yes	3 759/16 109	23.3	3 095/16 126	19.2	17.8%	1.28 (1.22 -1.35)	0.053
Written protocols for sucrose analgesia	Yes	3 663/15 325	23.9	3 155/15 508	20.3	14.9%	1.23 (1.17 -1.30)	
	No	598/ 3 628	16.5	308/ 3 551	8.7	47.4%	2.08 (1.80 -2.41)	**<10-3**
Parental presence authorized 24-hours	No	2 510/ 11 949	21.0	2 091/12 023	17.4	17.2%	1.26 (1.18 -1.35)	
	Yes	1 751/ 7 004	25.0	1 372/ 7 036	19.5	22.0%	1.28 (1.27 -1.49)	0.102
Night head nurse	No	2 843/12 348	23.0	2 399/12 889	18.6	19.2%	1.31 (1.23 -1.39)	
	Yes	1 418/ 6 605	21.5	1 064/ 6 170	17.2	19.7%	1.31 (1.20 -1.43)	0.955
Teaching status	Minor	1 798/ 7 222	24.9	1 511/ 7516	20.1	19.2%	1.32 (1.22 -1.42)	
	Major	2 463/11 731	21.0	1 952/11 543	16.9	19.5%	1.31 (1.22 -1.40)	0.864

[a] If positive, analgesia was higher during daytime [b] p value < 0.05 indicates that the factor modified the difference in analgesia use between daytime and nighttime in univariate
[c] related to admission

Table 5– Significant interactions between differences in analgesia use during daytime and nighttime and characteristics of children, centers and procedures in a multivariate, multilevel analysis[a]

Factor	Interaction test (p-value)	Interaction direction		OR
		Increase difference[c]	Decrease difference[c]	
Day of procedure[b]	<0.001	D2-D14		1.56 (1.24-1.95)
Mechanical ventilation	<0.05	Absence of mechanical ventilation during procedure		1.20 (1.02-1.43)
Parental presence	<0.001		Parents present	0.58 (0.44-0.78)
Nurse shift	<0.01	12 hour nurse shifts		1.42 (1.05-5.55)
Written protocols for sucrose analgesia	<0.001	Absence of written protocols for sucrose analgesia		2.44 (1.56-3.70)

[a] This is a multilevel analysis. The exposure was time of procedure (daytime versus nighttime). Factors in level 1 (associated with procedure) were day of procedure, mechanical ventilation, parental presence and continuous analgesia. Factors in level 2 (associated with children) were surgery, sex and gestational age. Factors in level 3 (associated with center) were nurse shift, nurse rotation, pain coordinator, written protocols for sucrose analgesia, parental presence authorized 24-hours, night head nurse and teaching status). Interactions between each factor and daytime versus nighttime were included in the model. Only factors that significantly interacted with time of procedure are shown in the table.

[b] related to admission

[c] Refers to the difference in analgesia use during daytime compared to nighttime

Neonatal Pain Management is not the same During Days and Nights in Intensive Care Units

Authors : Romain Guedj[1], MD, Claude Danan[2], MD, Patrick Daoud[3], MD, Véronique Zupan[4], MD, Sylvain Renolleau[5], MD, PhD, Elodie Zana[6], MD, Sophie Aizenfisz[7], MD, Alexandre Lapillonne[8], MD, PhD, Laure de Saint Blanquat[9], MD, Michèle Granier[10], MD, Philippe Durand[11], MD, Florence Castela[12], MD, Anne Coursol[13], MD, Philippe Hubert[14], MD, PhD, Patricia Cimerman[15], Research Nurse, Babak Khoshnood[16], PhD, KJS Anand[17], MD, PhD, Ricardo Carbajal[18], MD, PhD.

[1] Inserm U-953, 75020 Paris ; AP-HP, Hôpital Armand-Trousseau, Service d'urgences pédiatriques, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France
M.D.

[2] Centre Hospitalier Intercommunal de Créteil, Unité de réanimation néonatale et soins intensifs, 40 avenue de Verdun 94010 Créteil Cedex, France
M.D.

[3] Centre HospitaIier André Grégoire, Réanimation infantile, 56, bd de la Boissiere 93105 Montreuil-sous-Bois Cedex, France
M.D.

[4] AP-HP, Hôpital Antoine Béclère, Pédiatrie et Réanimation Néonatale, 157, rue de la Porte de Trivaux 92141 Clamart cedex, France
M.D.

[5] AP-HP, Hôpital Armand-Trousseau, Réanimation Néonatale et Pédiatrique, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France
PhD

[6] Maternité Port-Royal, Réanimation néonatale, 123 boulevard Port Royal, 75014 Paris, France

M.D.

[7] AP-HP, Hôpital Robert Debré, Réanimation et Surveillance continue pédiatrique, 48 boulevard sérurier 75019 Paris, France

M.D.

[8] Université Paris Descartes, AP-HP, Hôpital Necker-Enfants Malades, Réanimation Néonatale, 149 rue de Sèvres 75015 Paris, France

Ph.D

[9] AP-HP, Hôpital Necker-Enfants Malades, Réanimation Polyvalent Pédiatrique, 7149 rue de Sèvres, 75015 Paris, France

M.D.

[10] Centre Hospitalier Sud Francilien, Médecine Néonatale, 116 boulevard Jean Jaurès, 91100 Corbeil, France

M.D.

[11] AP-HP, Hôpital Bicêtre, Réanimation Néonatale et Pédiatrique, 78 rue du général Leclerc, 94275 Kremlin-Bicêtre, France

M.D.

[12] Centre Hospitalier Intercommunal, Hôpital Poissy, Unité de Réanimation Néonatale, 23 boulevard Gambetta, 78100 Poissy, France

M.D.

[13] Centre Hospitalier René Dubos, Médecine Néonatale et Réanimation Pédiatrique, 6 avenue de l'Ile de France, 95303 Pontoise, France

M.D.

[14] AP-HP, Hôpital Necker-Enfants Malades, Réanimation Polyvalent Pédiatrique, 149 rue de Sèvres, 75015 Paris, France

PhD

[15] AP-HP, Hôpital Armand-Trousseau, Centre Nationale de Ressources de lutte contre la Douleur26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France

RN (Research nurse)

[16] Inserm U953, Maternité Port-Royal, , 123 boulevard Port Royal, 75014 Paris, France

PhD

[17] University of Tennessee Health Science Center & Le Bonheur Children's Hospital, Memphis, TN

PhD

[18] Inserm U-953, 75020 Paris ; AP-HP, Hôpital Armand-Trousseau, Service d'urgences pédiatriques, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12, France; Université Pierre et Marie Curie, 75006 Paris

PhD

Corresponding author : Romain GUEDJ, Service des urgences pédiatriques, Hôpital Trousseau, 26 avenue du Dr Arnold Netter, 75571, Paris Cedex 12

Phone: + 33 144 736 487 Fax: +33 144 736 985

Email : romainguedj@gmail.com

Abbrévations :

NICU : Neonatal intensive care unit

OR : Odd ratio

PICU : Pediatric intensive care unit

Key words :

Pain ; Neonate ; Neonatology and infant care ; After-hours care ; painful procedures ; pain

Word count : 2 717~~492~~ words.

Abstract

Objective : To determine whether analgesic use for painful procedures performed in neonates in the Neonatal intensive care unit (NICU) differs during nights and days and during each of the 6-hour period of the day.

Design : Conducted as part of the prospective observational EPIPPAIN study which was designed to collect in real time and around-the-clock bedside data on all painful or stressful procedures

Setting : 13 NICUs and PICUs in the Paris Region, France.

Participants: All 430 neonates admitted to the participating units during a 6-week period between September 2005 and January 2006.

Data collection. During the first 14 days of admission data were collected on all painful procedures and analgesic therapy. The five most frequent procedures representing 38012 of all 42413 (90%) painful procedures were analyzed.

Intervention : Observationnal study

Main outcome assesment : We compared the use of specific analgesia for procedures performed during each of the 6-hour periods of a day: Morning (7:00AM to 12:59PM), Afternoon, Early Night and Late Night, and during Daytime (Morning+Afternoon) and Nighttime (Early Night+Late Night).

Results: 7724 out of 38012 (20.3%) painful procedures were carried out with a specific analgesic treatment. For Morning, Afternoon, Early Night and Late night, respectively, the use of analgesia was 25.8%, 18.9%, 18.3% and 18%. The relative reduction of analgesia was 18.3%, $p<0.01$~~01~~, between Daytime and Nighttime and 28.8%, $p<0.001$, between Morning and the Rest of the day. Parental presence, nurse 8-hour shifts and written protocols for analgesia were associated with a decrease in this difference.

Conclusion : The substantial differences in the use of analgesia around-the clock may be questioned on quality of care grounds.

Article summary :

Article focus : Some epidemiological studies focused on mortality-risk and medical errors raise concern about the homogeneity of care around the clock. Variation of analgesic use for painful procedure in neonates in intensive care units during day has never been studied.

Key messages : Specific analgesia for paiful procedures was more frequent during daytime than nighttime. It gradually decreased from morning to late night. Pain management guidelines should include standardization of care across 24 hours.

Main strenghts and limitations of this study : This is the first prospective multicenter study to show variations in analgesic practices around-the clock. The around the clock variations in analgesia use for procedural pain management did not correspond to an isolated practice of a single center but rather to the practices of a large geographical region.

Patients and their families expect that the same quality of care be provided to patients 24 hour-a-day. In reality, some epidemiological studies, mainly focused on mortality-risk and medical errors have found poorer outcomes for hospital care given during evening or night-time hours.[1–7] Among neonates, one study reported that perinatal mortality rates fluctuated according to the hour of birth with a peak occurring in the evening[3] and another study found a higher mortality for term neonates born in the evenings, nights or weekends.[4] These studies raise concern about the homogeneity of care in settings where patients expect safe and high quality care 24 hour-a-day. Significant practice variability also occurs in many other aspects of care. To our knowledge, the variation of neonatal pain management during day and night shifts has not been studied yet.

Neonatal pain management has received much attention during the last two decades leading professional societies to issue guidelines to improve pain management in this vulnerable population.[8,9] These guidelines highlight the necessity to improve analgesia for invasive procedures, which constitute the main source of pain in sick or premature infants admitted to the neonatal intensive care unit (NICU). However, surveys of clinical practices suggest that many evidence-based interventions have not been applied effectively in NICUs[10] and that wide gaps exist between knowledge and practice.[11] The undertreatment of pain in this population would be aggravated by variations in analgesic use according to the time of the day. Thus, the question about variation of quality of pain management during day and night is of practical relevance.

We designed this study to determine whether analgesic use for painful procedures performed in neonates in the NICU and the Pediatric intensive care unit (PICU) differs during nights and days and during four 6-hour periods of the day. This study was conducted as part of the EPIPPAIN study.[12]

METHODS

Study centers

The detailed methodology of the EPIPPAIN study was published elsewhere[12]. EPIPPAIN was a prospective observational study designed to collect 24-hours a day bedside data on all painful or stressful procedures performed in neonates admitted to NICUs and PICUs of a geographically defined region. All 14 tertiary care centers, NICUs and PICUs in the Paris Region were invited to participate and 13 accepted the invitation.

All the participating units had developed their pain management protocols locally. No instructions were given to modify the standard of care for procedural pain management in neonates. The study protocol and the data collection forms were reviewed by the local committee for the protection of human subjects.

Study population

We included in this study all neonates admitted to the participating units during a 6-week period between September 2005 and January 2006. Inclusion criterion was admitted preterm neonates younger than 45 postconceptional weeks and term neonates younger than 28 days. There were no exclusion criteria.

Data collection

During the first 14 days of admission to the participating units, prospective data were collected on all neonatal procedures causing pain, stress, or discomfort with the corresponding analgesic therapy. Specific pre-procedural analgesia included nonpharmacological (eg, sweet solutions, sucking) or pharmacological treatments (eg, single- or multiple drug doses). Nursing and medical staff at the bedside recorded all procedures on a specific form in real

time. ~~Since the EPIPPAIN study did not include data about the characteristics of the participating units, we conducted a phone survey with each head nurse in March 2010.~~ Since the EPIPPAIN study did not include data about the characteristics of the participating units, we conducted in March 2010 a phone survey with each head nurse present at the time of the initial study (2005-2006). We inquired about nurse shifts (two or three per day), shift rotation (between day and night), existence of a pain coordinator, written standardized protocols for sucrose analgesia, parental presence authorized 24-hours a day, ratios of residents to number of beds in order to describe the teaching status,[~~13~~13] and existence of a night head nurse.

Painful procedures

The EPIPPAIN study collected data on 430 neonates who underwent 60969 procedures. Because the current international definition of pain[~~14~~14] does not apply to neonates, we chose a published empirical approach to define pain. This describes pain as an inherent quality of life that appears early in ontogeny to serve as a signaling system for tissue damage.[15] Thus, a procedure was considered painful if it invaded the neonate's bodily integrity, causing skin injury or mucosal injury from the introduction or removal of foreign material into airway or digestive or urinary tract. Of these 60969 procedures, 42413 were considered painful, including 44 different procedures. In order to study the differences in analgesic management during the 24 hours of the day, we selected the five most frequent procedures that would both be readily performed at any time in an intensive care unit and also represent the majority of painful procedures : nasal or tracheal suctioning, heel sticks, adhesive removals, and vascular punctures (arterial punctures, venipunctures and intravenous cannulas). As shown in figure 1, these five procedures accounted for 90% of all painful procedures.

The use of procedural analgesia was defined as the use of specific analgesia given prior to painful procedures (pharmacological or nonpharmacological therapy).

Data analysis

Data were double entered into a relational database (EpiData Entry, version 3·0, Odense, Denmark) and analyzed with SPSS, v14 for Windows, (SPSS Inc, Chicago, Illinois) and Stata v.10.0 software (Stata Corporation, College Station, TX, USA). Procedures were distributed according to the time when they were performed, into four 6-hour periods: Morning (from 7:00AM to 12:59PM), Afternoon (from 1:00PM to 6:59PM), Early Night (from 7:00PM to 0:59AM) and Late Night (from 1:00AM to 6:59AM). We also defined Daytime as Morning + Afternoon and Nighttime as Early Night + Late Night. These timings were chosen because in France most of the day and night nurse shifts start at 7:00am and 7:00pm, respectively. Descriptive statistics were used to summarize continuous and categorical variables.

The outcome was the use of procedural analgesia. We calculated the percentage of use of ~~specific~~ procedural analgesia for each of the 6-hour periods, Daytime, Nighttime and for the period including Afternoon + Early Night + Late Night. Since data were not independent, procedures were clustered by child and center. Therefore, t~~T~~he use of ~~specific~~ procedural analgesia was compared ~~between~~ across periods using ~~Chi2-tests~~ a multilevel model with random effect at child and center levels.

We assessed changes in the effect of time of day across center by computing specific center crude OR to test heterogeneity of the ORs across centers. Then, we~~We~~ constructed a model including~~included~~ ~~in our model~~ procedures and children characteristics that were found to be associated with the use of specific analgesia prior to procedures in the EPIPPAIN study (Day of procedure, mechanical ventilation, parental presence, continuous analgesia, surgery, sex, and gestational age) and variables describing centers (nurse shift, nurse rotation, pain coordinator, written protocols for sucrose analgesia, policy on parental presence authorized 24-hours, night head nurse and teaching status). In order to investigate factors associated with differences in analgesia use 24-hours a day, we tested the interactions between analgesia use

and the characteristics of newborns, centers, and procedures. ~~Since data were not independent, procedures were clustered by child and center~~. We used a multilevel logistic regression model with random intercept and random slope ~~,~~ in order ~~to adjust interactions,~~ to test cross level interactions and to control for confounding factors.[16,17] ~~15,16.~~ In this multilevel analysis, procedure, child and center were at the lowest, second and highest level, respectively.

All the described factors were included in our model and all interactions between time of procedures (daytime or nighttime) and each covariate were obtained. Results are presented as point estimate odds ratios (ORs) with 2-sided 95% confidence intervals (CI). The threshold for statistical significance was set up at a probability value of <0.05.

RESULTS

From the 430 neonates included in the study, 309 (71.9%) were from NICUs and 121 (28.1%) from PICUs. The mean (SD) length of stay was 8.4 (4.6) calendar days and the observation period represented 3598 patient-days. The overall rate of mechanical tracheal ventilation was 70.5%, but it varied from 46.2% to 92% across units. Table 1 lists the demographic characteristics of the study population and Table 2 lists the characteristics of the participating centers. Appendix 1 ~~Figure 2~~ shows the distribution of painful procedures by hour of the day.

~~Specific Analgesic treatments~~

Overall, 7724 out of 38012 (20.3%) painful procedures were carried out with the provision of a specific analgesic treatment. Regarding heel sticks and vascular punctures, 3696/8396 (44.0%) and 1483/2088 (71.0%), respectively, were performed with specific analgesia. ~~Analgesic treatment varied widely among centers. Table 3 shows the use of specific analgesia, by center, for all procedures, heel sticks and vascular punctures.~~

Analgesia use according to time of the day

For Morning, Afternoon, Early Night and Late Night, respctively, the use of analgesia was 25.8%, 18.9%, 18.3% and 18% (p< 0.001). Figure 23 shows the use of analgesia for each 6-hour period of the day by category of procedures. For all painful procedures taken together or for skin-breaking procedures, the use of analgesia was higher in the morning, decreased during the day and was lowest in the late night. ~~(p<0.001). For Morning, Afternoon, Early Night and Late night, respectively, the use of analgesia was 25.8%, 18.9%, 18.3% and 18%~~

For all procedures taken together or for skin breaking procedures analyzed separately, the use of analgesia was significantly higher for procedures performed in the morning versus the rest of the day, (p<0.001 for all painful procedures, p<0.01 for heel sticks and vascular punctures), as well as for all painful procedures (p<0.01) and heel sticks (p<0.05) performed during the daytime versus the nighttime~~, p<0.001~~, Use of analgesia was close to be significantly higher for vascular punctures performed during daytime versus nightime (p = 0.07). -Table 34.

~~Clinical~~ Factors associated with Diurnal Variations in Analgesia

Use of analgesia varied widely among centers (from 4.0% to 49.8%) as shown in appendix 2. Moreover, difference of use analgesia between daytime and nighttime significantly varied among centers as shown in figure 3.

Interactions between differences in analgesia use during daytime and nighttime and the characteristics of children, centers and procedures in univariate analysis are listed in Table 45.~~-~~ We can see for instance that regarding mechanical ventilation the relative reduction in analgesia use during nighttime compared to daytime was 13.1% in invasively ventilated infants and 20.8% in spontaneously breathing or non-invasively ventilated infants.

The inclusion of all clinical factors in a multilevel analysis, showed that analgesia use was significantly higher for procedures performed during the daytime versus the nighttime, (OR =

2.25 ~~11~~[1.108 – 4.60~~3.78~~], p< 0.05). In this multilevel model, day of procedure (related to admission), mechanical ventilation, parental presence, nurse shift, and written protocol for analgesia significantly interacted with time of procedure, as shown in table 5~~6~~. (the whole list of ORs from the model is shown in appendix 3). Presence of parents reversed the difference of use of analgesia between daytime and nighttime; i.e. analgesia was significantly more frequent in nighttime than in daytime when parents were presents.

DISCUSSION

This is the first prospective multicenter study to show variations in analgesic practices around-the clock. The use of specific analgesia for painful procedures was more frequent during daytime than nighttime. Moreover, we found a sharp decrease in use of analgesia from morning to afternoon followed by a gentle decline thereafter.~~that specific analgesia for painful procedures was the highest in the morning and the lowest in the nighttime. In fact, it gradually decreased from morning to late night.~~

The relative reduction in the use of specific analgesia between daytime and nighttime was 18.3% for all five painful procedures and this difference reached 28.8% between the morning and the rest of the day. Such substantial differences in the use of analgesia may be questioned on quality of care grounds. We consider that the lower use of analgesia during those periods represents a marker of poor quality care that needs to be overcome. The differences in analgesia use between daytime and nighttime that we found in this study were independent of the type of procedure and whether the procedure was more frequently performed during a period of the day. In fact, heel sticks were homogeneously distributed around-the clock and vascular punctures were more frequent during the morning, but the differences in analgesia use were very similar and consistent (Appendix 1~~figure 3~~).

The around the clock variations in analgesia use for procedural pain management did not correspond to an isolated practice of a single center but rather to the practices of a large geographical region. The participation of all but one center in this region, the uniform data collection at all centers, and 100% patient inclusion during the study period ensure that the study cohort was representative of NICU procedural pain management in the Paris region. ~~Moreover, we feel that these results could be extrapolated to the entire French territory because this is the most populated region of France and it closely reflects the practices in the rest of the country~~The extrapolation of these results to the entire French territory may be possible but not totally certain because of conflincting arguments. On one side, (i) the Paris region is the most populated region in France and practices within this area closely may reflect those of the country and (ii) analgesia use was significantly more frequent during daytime than nighttime in eight of thirteen centers but on the other side, the analysis of crude OR by center did not show homogeneity (figure 3).

The variation of quality of neonatal care over the day has been rarely studied directly. Most studies have used outcomes as a proxy to assess this variation. Some studies reported increased rates of perinatal death at night[~~3–5~~ 3–5]. Although mortality could be considered as an important proxy to assess quality of care, it has the disadvantage of being related to only serious or critical conditions and it is exposed to several confounding factors. Medication error rate has also been used in a few studies to assess variations in quality of care. It has been found that errors were higher during nighttime than during daytime[6, 20]. However, care quality cannot be restricted to a safety problem. Optimal care quality implies, among other standards, care without pain. Thus, analgesic use for painful procedure is also a parameter to measure care quality.

In an attempt to explain our findings, we investigated factors associated with differences of analgesia use around-the-clock. Parental presence, nurse 8-hour shifts and written protocols for analgesia decreased the difference of analgesia use between day and night. These results suggest that written protocols or parental presence may limit the reduction of analgesia use during nighttime. Protocols limit the freedom of health care providers about the management of pain, making the practice of caregivers more homogeneous. It has been reported that the presence of protocols, by harmonizing practices, increases the quality of care.[10] ~~10.~~ Similarly, it has been reported that the presence of parents influences the practice of caregivers.[18] ~~17.~~ Our data also suggest that shorter hour shifts (8-hour) for nurses decrease the difference of analgesia use between day and night. In other health care areas, it has been shown that 12-hours shifts negatively influence the behavior of care providers yielding to less efficient care.[19,20] ~~18,19.~~ However, the area of variations in pain management practices is highly complex and to attempt to explain it by staffing or protocols is probably simplistic. Other factors that we have not studied could play a role. Contextual factors may influence staff behaviors. Although number of nurses is homogeneous during daytime and nighttime in French NICUs, more medical staff is around in the morning and in the afternoon. Interprofessional collaboration practices[21] ~~20~~ and higher access to personnel to care for complex patients[22] ~~21~~ may enhance pain practices. Thus, analgesic use may also be influenced by the total number of staff and not only nurses.

We acknowledge two limitations of this study. First, a potential bias would be a difference in quality of data collection during days and nights. We consider that this is not likely because we ensured a completeness of reporting by verifying from the patients' charts that all

procedures were documented on the study datasheets. Furthermore, there is no reason that a nurse recorded a procedure but not the use of analgelsia. Second, we collected data about the characteristics and organization of center in a retrospective manner 5 years after the collection of clinical data. This might have introduced a bias. However, we feel that this bias was minimized because we obtained data from the head nurse who usually keeps records of all organizational details. Since we only had 13 centers, data about organizational characteristics should be looked upon with caution.

CONCLUSION

Our findings suggest that the constant efforts to improve care quality should also include standardization of care across 24 hours and pain management guidelines should reinforce this message. The variation of care quality during the day is certainly a complex phenomenon that deserves further research. It appears that human factors intervene in the process of care delivery and we need to better understand them in order to improve care quality. Our results suggest that the modification of organisational factors such as parental presence and written protocols may contribute to the homogenization of quality of care around the clock.

Aknowledgment

We would like to aknowledge l'Académie de Médecine

REFERENCES

1 Duke GJ, Green JV, Briedis JH. Night shift discharge from intensive care unit increases the mortality risk of ICU survivors. *Anaesth Intensive Care* 2004;**32**:697–701.

2 Laupland KB, Shahpori R, Kirkpatrick AW, *et al.* Hospital mortality among adults admitted to and discharged from intensive care on weekends and evenings. *J Crit Care* 2008;**23**:317–24.

3 Paccaud F, Martin Béran B, Gutzwiller F. Hour of birth as a prognostic factor for perinatal death. *Lancet* 1988;**1**:340–3.

4 Pasupathy D, Wood AM, Pell JP, *et al.* Time of birth and risk of neonatal death at term: retrospective cohort study. *BMJ* 2010;**341**:c3498.

5 Stephansson O, Dickman PW, Johansson ALV, *et al.* Time of birth and risk of intrapartum and early neonatal death. *Epidemiology* 2003;**14**:218–22.

6 Miller AD, Piro CC, Rudisill CN, *et al.* Nighttime and weekend medication error rates in an inpatient pediatric population. *Ann Pharmacother* 2010;**44**:1739–46.

7 Hendey GW, Barth BE, Soliz T. Overnight and Postcall Errors in Medication Orders. *Academic Emergency Medicine* 2005;**12**:629–34.

8 Anand KJ. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med* 2001;**155**:173–80.

9 Prevention and management of pain and stress in the neonate. American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee. *Pediatrics* 2000;**105**:454–61.

10 Sharek PJ, Powers R, Koehn A, *et al.* Evaluation and development of potentially better practices to improve pain management of neonates. *Pediatrics* 2006;**118 Suppl 2**:S78–86.

11 Spence K, Henderson-Smart D. Closing the evidence-practice gap for newborn pain using clinical networks. *J Paediatr Child Health* 2011;**47**:92–8.

12 Carbajal R, Rousset A, Danan C, *et al.* Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA* 2008;**300**:60–70.

13 Aiken LH, Clarke SP, Sloane DM, *et al.* Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. *JAMA* 2002;**288**:1987–93.

14 Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. *Pain* 1979;**6**:249.

15 Merlo J, Chaix B, Ohlsson H, *et al.* A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *J Epidemiol Community Health* 2006;**60**:290–7.

16 Merlo J, Chaix B, Yang M, *et al.* A brief conceptual tutorial on multilevel analysis in social epidemiology: interpreting neighbourhood differences and the effect of neighbourhood characteristics on individual health. *J Epidemiol Community Health* 2005;**59**:1022–8.

17 Johnston C, Barrington KJ, Taddio A, *et al.* Pain in Canadian NICUs: have we improved over the past 12 years? *Clin J Pain* 2011;**27**:225–32.

18 Borges FN da S, Fischer FM. Twelve hour night shifts of healthcare workers: a risk to the patients? *Chronobiol Int* 2003;**20**:351–60.

19 Macias DJ, Hafner J 2nd, Brillman JC, *et al.* Effect of time of day and duration into shift on hazardous exposures to biological fluids. *Acad Emerg Med* 1996;**3**:605–10.

20 Latimer MA, Johnston CC, Ritchie JA, *et al.* Factors affecting delivery of evidence-based procedural pain care in hospitalized neonates. *J Obstet Gynecol Neonatal Nurs* 2009;**38**:182–94.

21 Stevens B, Riahi S, Cardoso R, *et al.* The influence of context on pain practices in the NICU: perceptions of health care professionals. *Qual Health Res* 2011;**21**:757–70.

1. Duke GJ, Green JV, Briedis JH. Night-shift discharge from intensive care unit increases the mortality-risk of ICU survivors. Anaesth Intensive Care. oct 2004;32(5):697–701.

2. Laupland KB, Shahpori R, Kirkpatrick AW, Stelfox HT. Hospital mortality among adults admitted to and discharged from intensive care on weekends and evenings. J Crit Care. sept 2008;23(3):317–324.

3. Paccaud F, Martin-Béran B, Gutzwiller F. Hour of birth as a prognostic factor for perinatal death. Lancet. 13 févr 1988;1(8581):340–343.

4. Pasupathy D, Wood AM, Pell JP, Fleming M, Smith GCS. Time of birth and risk of neonatal death at term: retrospective cohort study. BMJ. 2010;341:c3498.

5. Stephansson O, Dickman PW, Johansson ALV, Kieler H, Cnattingius S. Time of birth and risk of intrapartum and early neonatal death. Epidemiology. mars 2003;14(2):218–222.

6. Miller AD, Piro CC, Rudisill CN, Bookstaver PB, Bair JD, Bennett CL. Nighttime and weekend medication error rates in an inpatient pediatric population. Ann Pharmacother. nov 2010;44(11):1739–1746.

7. Hendey GW, Barth BE, Soliz T. Overnight and Postcall Errors in Medication Orders. Academic Emergency Medicine. 1 juill 2005;12(7):629–634.

8. Anand KJ. Consensus statement for the prevention and management of pain in the newborn. Arch Pediatr Adolesc Med. févr 2001;155(2):173–180.

9. Prevention and management of pain and stress in the neonate. American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on

Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee. Pediatrics. févr 2000;105(2):454□461.

10. Sharek PJ, Powers R, Koehn A, Anand KJS. Evaluation and development of potentially better practices to improve pain management of neonates. Pediatrics. nov 2006;118 Suppl 2:S78□86.

11. Spence K, Henderson-Smart D. Closing the evidence-practice gap for newborn pain using clinical networks. J Paediatr Child Health. mars 2011;47(3):92□98.

12. Carbajal R, Rousset A, Danan C, Coquery S, Nolent P, Ducrocq S, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. JAMA. 2 juill 2008;300(1):60□70.

13. Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. JAMA. 23 oct 2002;288(16):1987□1993.

14. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. Pain. juin 1979;6(3):249.

15. Anand KJ, Craig KD. New perspectives on the definition of pain. Pain. sept 1996;67(1):3□6; discussion 209□211.

16. Merlo J, Chaix B, Ohlsson H, Beckman A, Johnell K, Hjerpe P, et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. J Epidemiol Community Health. avr 2006;60(4):290□297.

17. Merlo J, Chaix B, Yang M, Lynch J, Råstam L. A brief conceptual tutorial on multilevel analysis in social epidemiology: interpreting neighbourhood differences and the effect of neighbourhood characteristics on individual health. J Epidemiol Community Health. déc 2005;59(12):1022□1028.

18. Johnston C, Barrington KJ, Taddio A, Carbajal R, Filion F. Pain in Canadian NICUs: have we improved over the past 12 years? Clin J Pain. avr 2011;27(3):225□232.

19. Borges FN da S, Fischer FM. Twelve-hour night shifts of healthcare workers: a risk to the patients? Chronobiol Int. mars 2003;20(2):351□360.

20. Macias DJ, Hafner J 2nd, Brillman JC, Tandberg D. Effect of time of day and duration into shift on hazardous exposures to biological fluids. Acad Emerg Med. juin 1996;3(6):605□610.

21. Latimer MA, Johnston CC, Ritchie JA, Clarke SP, Gilin D. Factors affecting delivery of evidence-based procedural pain care in hospitalized neonates. J Obstet Gynecol Neonatal

Nurs. avr 2009;38(2):182□194.

22. Stevens B, Riahi S, Cardoso R, Ballantyne M, Yamada J, Beyene J, et al. The influence of context on pain practices in the NICU: perceptions of health care professionals. Qual Health Res. juin 2011;21(6):757□770.

Table 1. Demographic characteristics of 430 neonates

Characteristics	Number (%)	Mean (SD)	Median (IQR)	Range
Gestational age group at birth 24-29 wk 30-32 wk 33-36 wk 37-42 wk	 119 (27.7) 108 (25.1) 84 (19.5) 119 (27.7)			
Birth weight (g)		1962 (957)	1743 (1155-2738)	490-4760
Male	237 (55.1)			
Inborn (born at study hospital)	237 (55.1)			
Age at admission (h)			2.5 (0.5 – 24.0)	
Surgery during the study period	30 (7.0)			
Mechanical tracheal ventilation	303 (70.5)			
Duration of participation (d) Overall 24-29 wk 30-32 wk 33-36 wk 37-42 wk		 8.4 (4.6) 11.6 (3.8) 8.7 (4.6) 6.6 (4.0) 6.0 (3.9)	 8.0 (4.0-14.0) 14.0 (9.0-14.0) 9.0 (4.0-14.0) 6.0 (3.0-9.0) 5.0 (3.0-8.0)	 1-14 2-14 1-14 2-14 1-14
Hospitalized for more than 14 days	126 (29.3)			
Died during the study period	24(5.6)			

Table 2: Characteristics of centers

	Number of centers n = 13
Nurse shift	
2 per day	9
3 per day	4
Day-night nurse rotation	
Yes	7
No	6
Pain coordinator	
Yes	10
No	3
Written standardized protocols for sucrose analgesia	
Yes	11
No	2
Parental presence authorized 24-hours	
Yes	6
No	7
Teaching status*	
Minor	6
Major	7
Night head nurse	
Yes	2
No	11

* postgraduate trainees /bed ratio : minor teaching units if ratios were ¼ or less, major teaching units if ratios were higher than ¼

Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH· Hospital nurse staffing and patient mortality , nurse burnout, and job dissatisfaction. JAMA. 2002 Oct 23-30;288(16):1987-93

Table 3. Differences in use of analgesia for procedures performed in the morning versus the rest of the day and for procedures performed in daytime versus nighttime.

~~Table 3 – Use of specific analgesia for painful procedures by center~~

	~~Procedures carried out with specific preprocedural analgesia~~					
~~Center (n°)~~	~~All 5 painful procedures~~		~~Heel sticks~~		~~Vascular punctures~~	
	~~n/N*~~	~~%~~	~~n/N*~~	~~%~~	~~n/N*~~	~~%~~
~~1~~	~~89 / 1 356~~	~~6.6~~	~~3/ 8~~	~~37.5~~	~~35/ 67~~	~~52.2~~
~~2~~	~~162 / 4 091~~	~~4.0~~	~~22/ 926~~	~~2.4~~	~~114/ 207~~	~~55.1~~
~~3~~	~~1 614/ 3 239~~	~~49.8~~	~~939/ 1312~~	~~71.6~~	~~224/ 285~~	~~78.6~~
~~4~~	~~544 / 2 105~~	~~25.8~~	~~270/ 629~~	~~42.9~~	~~183/ 199~~	~~92.0~~
~~5~~	~~1 682 / 9 110~~	~~18.5~~	~~847/ 1 560~~	~~54.3~~	~~279/ 374~~	~~74.6~~
~~6~~	~~590/ 2 467~~	~~23.9~~	~~410/ 489~~	~~83.8~~	~~86/ 105~~	~~81.9~~
~~7~~	~~213 / 2 138~~	~~10.0~~	~~94/ 633~~	~~14.8~~	~~55/ 82~~	~~67.1~~
~~8~~	~~711 / 2 309~~	~~30.8~~	~~394/ 573~~	~~68.8~~	~~94/ 162~~	~~58.0~~
~~9~~	~~111 / 1 235~~	~~9.0~~	~~18/ 264~~	~~6.8~~	~~55/ 106~~	~~51.9~~
~~10~~	~~331 / 1 953~~	~~16.9~~	~~109/ 360~~	~~30.3~~	~~53/ 84~~	~~63.1~~
~~11~~	~~237 / 2316~~	~~10.2~~	~~140/ 643~~	~~21.8~~	~~43/ 75~~	~~57.3~~
~~12~~	~~200 / 983~~	~~20.3~~	~~87/ 241~~	~~36.1~~	~~37/ 60~~	~~61.7~~
~~13~~	~~1 240 / 4710~~	~~26.3~~	~~363/ 758~~	~~47.9~~	~~225/ 282~~	~~79.8~~
~~All centers~~	~~7 724/ 38 012~~	~~20.3~~	~~3 696/ 8 396~~	~~44.0~~	~~1 483/ 2088~~	~~71.0~~

	Number of procedures	Procedures carried out with specific analgesia		Relative Reduction *	Univariate analysis
	N	n	%		p
MORNING VS REST OF THE DAY					
5 painful procedures					
Morning	9 861	2 546	25.8%		
Rest of the day	28 151	5 178	18.4%	28.8 %	**<0.001**
Heel sticks					

Morning	1 860	980 52.7%		
Rest of the day	6 536	2 716 41.6%	21.1 %	**<0.01**
Vascular punctures				
Morning	955	723 75.7%		
Rest of the day	1 133	760 67.1%	11.4 %	**<0.01**
DAYTIME VS NIGHTTIME				
5 painful procedures				
Daytime	19 059	4 261 22.5%		
Nighttime	18 953	3 463 18.3%	18.3 %	**<0.01**
Heel sticks				
Daytime	3 871	1 856 47.9%		
Nighttime	4 525	1 840 40.7%	15.2 %	**<0.05**
Vascular punctures				
Daytime	1 363	1 003 73.6%		
Nighttime	725	480 66.2%	10.0 %	**0.07**

~~* Number of painful procedures performed with analgesia / total number of that specific procedure~~

Table 4. Differences in use of analgesia for procedures performed in the morning versus the rest of the day and for procedures performed in daytime versus nighttime.

	Number of procedures N	Procedures carried out with specific analgesia n %	Relative Reduction * 	p (chi2)
MORNING VS REST OF THE DAY				
5 painful procedures				
Morning	9 861	2 546 25.8%		
Rest of the day	28 151	5 178 18.4%	28.8 %	**<0.001**
Heel sticks				
Morning	1 860	980 52.7%		
Rest of the day	6 536	2 716 41.6%	21.1 %	**<0.001**
Vascular punctures				
Morning	955	723 75.7%		
Rest of the day	1 133	760 67.1%	11.4 %	**<0.001**
DAYTIME VS NIGHTTIME				
5 painful procedures				
Daytime	19 059	4 261 22.5%		
Nighttime	18 953	3 463 18.3%	18.3 %	**<0.001**
Heel sticks				
Daytime	3 871	1 856 47.9%		
Nighttime	4 525	1 840 40.7%	15.2 %	**<0.001**
Vascular punctures				
Daytime	1 363	1 003 73.6%		
Nighttime	725	480 66.2%	10.0 %	**<0.001**

*Percentage of relative reduction in the use of specific analgesia

**These are results from multilevel analysis with time of day as the only explanatory variable. In this multilevel analyses, procedure, child and center were at the lowest, second and highest level, respectively.

Table 4~~5~~ - Interactions between differences in analgesia use during daytime and nighttime and characteristics of children, centers and procedures in univariate analysis

Factor		UNIVARIATE ANALYSIS						
		Procedures carried out with specific analgesia				Daytime compared to nightime : Relative reduction[a]	Daytime compared to nightime : OR	Interaction test (p)[b]
		Daytime		Nightime				
		n/N	%	n/N	%			
Day of procedure[c]	D1	272/ 1 789	15.2	276/ 1 667	16.6	-8.9%	0.90 (0.75 -1.09)	
	D2-D14	3 989/17 164	23.2	3 187/17 392	18.3	21.2%	1.35 (1.28 -1.42)	**<10.3**
Mechanical ventilation	Yes	1 668/11 908	14.0	1 501/12 327	12.2	13.1%	1.18 (1.09 -1.27)	
	No	2 593/ 7 045	36.8	1 962/ 6 732	29.1	20.8%	1.42 (1.32 -1.52)	**<10-3**
Parental presence	Yes	331/ 1 488	22.2	131/ 485	27.0	-21.4%	0.77 (0.61 -0.98)	
	No	3 930/17 465	22.5	3 332/18 574	17.9	21.0%	1.33 (1.26 -1.40)	**<10-3**
Continuous analgesia	Yes	738/ 6 341	11.6	722/ 6 864	10.8	9.6 %	1.12 (1.01 -1.25)	
	No	3 523/12 612	27.9	2 741/12 195	22.5	19.5 %	1.34 (1.26 -1.42)	**0.005**
Surgery	Yes	337/ 1 576	21.4	300/ 1 714	17.5	18.2%	1.28 (1.08 -1.53)	
	No	3 924/17 377	22.6	3 163/17 345	18.2	19.5%	1.31 (1.24 -1.38)	0.829
Sex	Male	2 363/10 758	22.0	1 877/10 757	17.4	20.9%	1.33 (1.25 -1.43)	
	Female	1 898/ 8 198	23.2	1 586/ 8 302	19.1	17.6%	1.28 (1.18 -138)	0.410
Gestational age	≥ 37 weeks	583/ 3 803	15.3	435/ 3 796	11.5	25.2%	1.40 (1.22 -1.60)	
	< 37 weeks	3 678/15 150	24.3	3 028/15 263	19.8	18.3%	1.30 (1.23 -1.37)	0.295
Nurse shift	3 per day	1 634/ 5 995	27.3	1 276/ 5 907	21.6	20.7%	1.36 (1.25 -1.48)	
	2 per day	2 627/12 958	20.3	2 187/13 152	16.6	18.0%	1.28 (1.20 -1.36)	0.230
Nurse rotation	No	1 853/ 7 507	24.7	1 477/ 7 704	19.2	22.3%	1.38 (1.28 -1.49)	
	Yes	2 408/11 446	21.0	1 986/11 355	17.5	16.9%	1.26 (1.18 -1.34)	0.068
Pain coordinator	No	502/ 2 844	17.7	368/ 2 933	12.5	28.9%	1.49 (1.29 -1.73)	
	Yes	3 759/16 109	23.3	3 095/16 126	19.2	17.8%	1.28 (1.22 -1.35)	0.053
Written protocols for sucrose analgesia	Yes	3 663/15 325	23.9	3 155/15 508	20.3	14.9%	1.23 (1.17 -1.30)	
	No	598/ 3 628	16.5	308/ 3 551	8.7	47.4%	2.08 (1.80 -2.41)	**<10-3**
Parental presence authorized 24-hours	No	2 510/ 11 949	21.0	2 091/12 023	17.4	17.2%	1.26 (1.18 -1.35)	
	Yes	1 751/ 7 004	25.0	1 372/ 7 036	19.5	22.0%	1.28 (1.27 -1.49)	0.102
Night head nurse	No	2 843/12 348	23.0	2 399/12 889	18.6	19.2%	1.31 (1.23 -1.39)	
	Yes	1 418/ 6 605	21.5	1 064/ 6 170	17.2	19.7%	1.31 (1.20 -1.43)	0.955
Teaching status	Minor	1 798/ 7 222	24.9	1 511/ 7516	20.1	19.2%	1.32 (1.22 -1.42)	
	Major	2 463/11 731	21.0	1 952/11 543	16.9	19.5%	1.31 (1.22 -1.40)	0.864

[a] If positive, analgesia was higher during daytime [b] p value < 0.05 indicates that the factor modified the difference in analgesia use between daytime and nighttime in univariate
[c] related to admission

Table 65 – Significant interactions between differences in analgesia use during daytime and nighttime and characteristics of children, centers and procedures in a multivariate, multilevel analysis[a]

Factor	Interaction test (p-value)	Interaction direction		OR
		Increase difference[c]	Decrease difference[c]	
Day of procedure[b]	<0.001	D2-D14		1.565 (1.243-1.954)
Mechanical ventilation	<0.05	Absence of mechanical ventilation during procedure		1.201 (1.02-1.43)
Parental presence	<0.001		Parents present	0.589 (0.44-0.789)
Nurse shift	<0.01	12 hour nurse shifts		1.422.25 (1.0523-5.554.12)
Written protocols for sucrose analgesia	<0.001	Absence of written protocols for sucrose analgesia		2.440 (1.5674-3.7030)

[a] This is a multilevel analysis. The exposure was time of procedure (daytime versus nighttime). Factors in level 1 (associated with procedure) were day of procedure, mechanical ventilation, parental presence and continuous analgesia. Factors in level 2 (associated with children) were surgery, sex and gestational age. Factors in level 3 (associated with center) were nurse shift, nurse rotation, pain coordinator, written protocols for sucrose analgesia, parental presence authorized 24-hours, night head nurse and teaching status). Interactions between each factor and daytime versus nighttime were included in the model. Only factors that significantly interacted with time of procedure are shown in the table.

[b] related to admission

[c] Refers to the difference in analgesia use during daytime compared to nighttime

Funding source and conflict of interest statement : This study was supported by grant funds from the Fondation CNP, and the Fondation de France, France. R Guedj received a grant from L'Académie de Médecine to work on this study. These funding agencies did not participate in any of the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. No financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work

Data Sharing : No available data sharing

Contributor's statement page

Romain Guedj : Dr Guedj analysed and interpreted the data. He drafted the initial manuscripted and approved the final manuscript as submitted.

Claude Danan : Dr Danan implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Patrick Daoud : Dr Daoud implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Véronique Zupan : Dr Zupan implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Sylvain Renolleau : Pr Renolleau implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Elodie Zana : Dr Zana implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Sophie Aizenfisz : Dr Aizenfisz implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Alexandre Lapillonne : Dr Lapillone implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Laure de Saint Blanquat : Dr de Saint Blanquat implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Michèle Granier : Dr Granier implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Philippe Durand : Dr Durand implemeted, coordinated and supervised the trial at one of thirteen particpating unit. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Florence Castela : Dr Castela implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Anne Coursol : Dr Coursol implemeted, coordinated and supervised the trial at one of thirteen particpating unit. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Philippe Hubert : Pr Hubert designed the study. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Patricia Cimerman : Mrs Cimerman designed the study. She reviewed and revised the manuscript, and she approved the final manuscript as submitted.

Babak Khoshnood : Pr Khoshnood designed the study and interpreted the data. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

KJS Anand : Pr Anand designed the study. He reviewed and revised the manuscript, and he approved the final manuscript as submitted.

Ricardo Carbajal : Pr Carbajal designed the study and interpreted the data. He reviewed and revised the manuscript, and he approved the final manuscript as submitted. He is guarantor

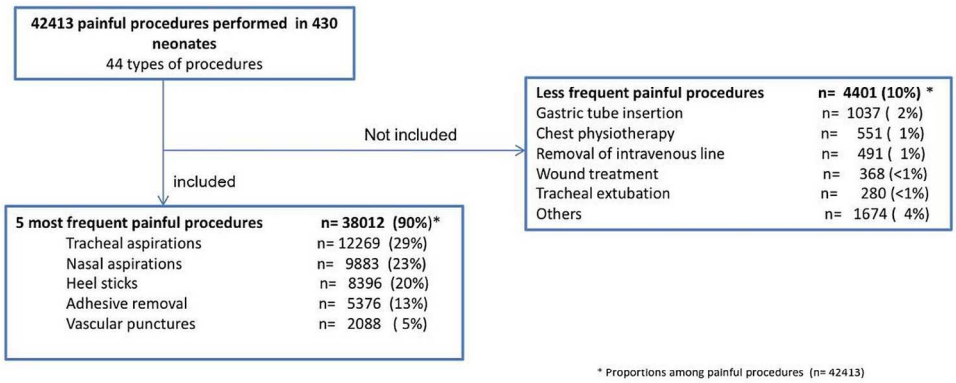


Figure 1 – Distribution of painful procedures analysed in the study

119x90mm (300 x 300 DPI)

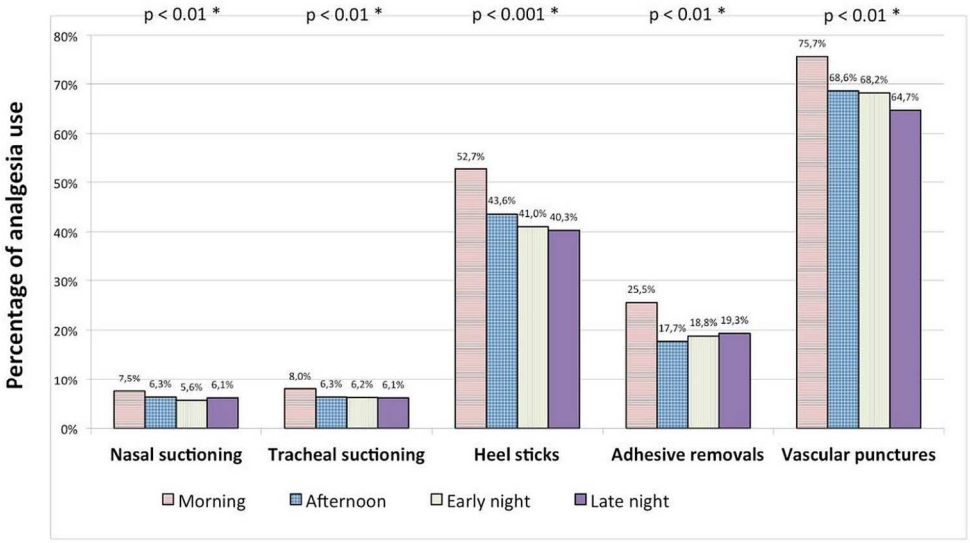


Figure 2 – Use of analgesia during each of the 6-hour period of the day by category of procedure

120x90mm (300 x 300 DPI)

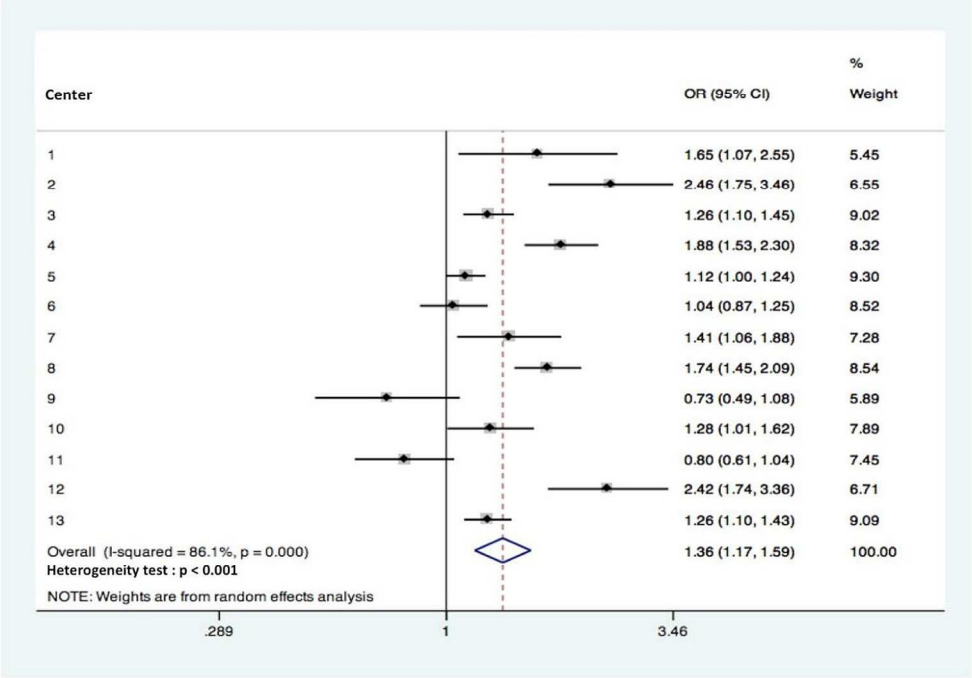
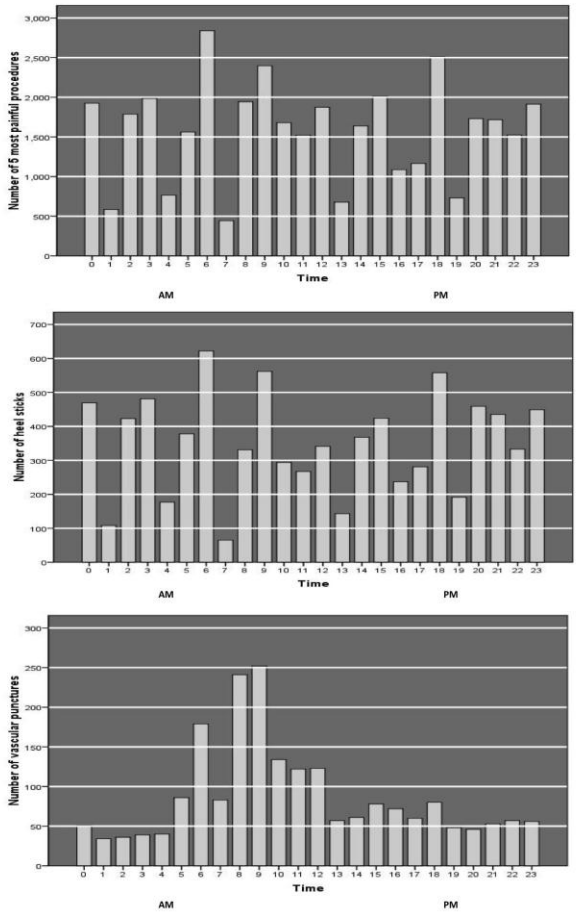


Figure 3 Use of analgesia for procedures performed in daytime versus nighttime by centers; Test of heterogeneity – p<0.001.

119x90mm (300 x 300 DPI)



Appendix 1 – Distribution of painful procedures by hour the day

(Five most frequent painful procedures, n=38 012
Heel sticks, n = 8 396
Vascular punctures, n = 2 088)

Appendix 2– Use of specific analgesia for painful procedures by center and by time of day

	Procedures carried out with specific preprocedural analgesia					
Center	All 5 painful procedures n/N* (%)		Heel sticks n/N* (%)		Vascular puncture n/N* (%)	
		By time of day D- Daytime N-Nighttime		By time of day D- Daytime N-Nighttime		By time of day D- Daytime N-Nighttime
1	89 / 1 356 (6.6)	D – 51/ 619 (8.2) N – 38/ 737 (5.2)	3/ 8 (37.5)	D – 1/ 2 (50.0) N – 2/ 6 (33.3)	35/ 67 (52.2)	D – 28/47 (59.6) N – 7/20 (35.0)
2	162 / 4 091 (4.0)	D – 113/2 015 (5.6) N – 49/2 076 (2.4)	22/ 926 (2.4)	D – 16/397 (4.0) N – 6/529 (1.1)	114/ 207 (55.1)	D – 79/149 (53.0) N – 35/ 58 (60.3)
3	1 614/ 3 239 (49.8)	D – 882/1 676 (52.6) N – 732/1 563 (5,2)	939/ 1312 (71.6)	D – 457/600 (76.2) N – 482/712 (67.7)	224/ 285 (78.6)	D – 154/183 (84.2) N – 70/102 (68.6)
4	544 / 2 105 (25.8)	D – 349/1 111 (31.4) N – 195/ 994 (19.6)	270/ 629 (42.9)	D – 151/315 (47.9) N – 119/314 (37.9)	183/ 199 (92.0)	D – 142/153 (92.8) N – 41/ 46 (89.1)
5	1 682 / 9 110 (18.5)	D – 905/4 700 (19.3) N – 777/4 410 (17.6)	847/ 1 560 (54.3)	D – 424/742 (57.1) N – 423/818 (51.7)	279/ 374 (74.6)	D – 141/193 (73.1) N – 138/181 (76.2)
6	590/ 2 467 (23.9)	D – 290/1 193 (24.3) N – 300/1 274 (23.5)	410/ 489 (83.8)	D – 176/221 (79.6) N – 234/268 (87.3)	86/ 105 (81.9)	D – 65/ 79 (82.3) N – 21/ 26 (80.8)
7	213 / 2 138 (10.0)	D – 117/1 009 (11.6) N – 96/1 129 (8.5)	94/ 633 (14.8)	D – 48/292 (16.4) N – 46/341 (13.5)	55/ 82 (67.1)	D – 47/ 66 (71.2) N – 8/ 16 (50.0)
8	711 / 2 309 (30.8)	D – 462/1 286 (35.9) N – 249/1 023 (24.3)	394/ 573 (68.8)	D – 266/367 (72.5) N – 128/206 (62.1)	94/ 162 (58.0)	D – 76/116 (65.5) N – 18/ 46 (39.1)
9	111 / 1 235 (9.0)	D – 46/ 601 (7.7) N – 65/ 634 (10.3)	18/ 264 (6.8)	D – 11/131 (8.4) N – 7/133 (5.3)	55/ 106 (51.9)	D – 16/ 42 (38.1) N – 39/ 64 (60.9)
10	331 / 1 953 (16.9)	D – 168/ 893 (18.8) N – 163/1 060 (15.4)	109/ 360 (30.3)	D – 57/135 (42.2) N – 52/225 (23.1)	53/ 84 (63.1)	D – 37/ 55 (67.3) N – 16/ 29 (55.2)
11	237 / 2316 (10.2)	D – 102/1 114 (9.2) N – 135/1 202 (11.2)	140/ 643 (21.8)	D – 53/288 (18.4) N – 87/355 (24.5)	43/ 75 (57.3)	D – 21/ 33 (63.6) N – 22/ 42 (52.4)
12	200 / 983 (20.3)	D – 136/ 502 (27.1) N – 64/ 48 (13.3)	87/ 241 (36.1)	D – 42/106 (39.6) N – 45/135 (33.3)	37/ 60 (61.7)	D – 28/ 41 (68.3) N – 9/ 19 (47.4)
13	1 240 / 4710 (26.3)	D – 640/2 234 (28.6) N – 600/2 476 (24.2)	363/ 758 (47.9)	D – 154/275 (56.0) N – 209/483 (43.3)	225/ 282 (79.8)	D – 169/206 (82.0) N – 56/ 76 (73.7)

*** Number of painful procedures performed with analgesia / total number of that specific procedure**

Appendix 3 : Factors Associated With the Use of Analgesia during the 5 most frequent painful procedures in neonates and interaction between time of day and the other factors.

Factors		OR	Interaction with time of the day OR
Time of the day	Night Day	1 **2.25 [1.10-4.60]**	
Day of procedure[c]	D1 D2-D14	1 **1.24 [1.05-1.45]**	1 1.56 [1.24-1.95]
Mechanical ventilation	No Yes	1 0.49 [0.43-0.56]	1 0.83 [0.70-0.98]
Parental presence	No Yes	1 **1.56 [1.22-2.00]**	1 0.58 [0.44-0.78]
Continuous analgesia	No Yes	1 **0.51 [0.44-0.60]**	1 0.93 [0.76-1.14]
Surgery	No Yes	1 1.49 [0.92-2.42]	1 1.01 [0.69-1.47]
Sex	Male Female	1 0.94 [0.75-1.17]	1 1.07 [0.90-1.29]
Gestational age	≥ 37 weeks < 37 weeks	1 1.19 [0.91-1.56]	1 0.84 [0.67-1.06]
Nurse shift	2 per day 3 per day	1 **12.78 [1.73-94.42]**	1 0.41 [0.18-0.95]
Nurse rotation	No Yes	1 2.02 [0.64-6.37]	1 0.74 [0.47-1.20]
Pain coordinator	No Yes	1 1.29 [0.50-3.33]	1 1.26 [0.86-1.86]
Written protocols for sucrose analgesia	No Yes	1 **3.50 [1.23-9.95]**	1 0.41 [0.27-0.64]
Parental presence authorized 24-hours	No Yes	1 0.37 [0.07-2.05]	1 1.92 [0.92-4.00]
Night head nurse	No Yes	1 0.91 [0.31-2.72]	1 1.51 [0.96-2.37]
Teaching status	Minor Major	1 0.59 [0.24-1.47]	1 0.81 [0.56-1.18]

This is a multilevel analysis. The exposure was time of procedure (daytime versus nighttime). Factors in level 1 (associated with procedure) were day of procedure, mechanical ventilation, parental presence and continuous analgesia. Factors in level 2 (associated with children) were surgery, sex and gestational age. Factors in level 3 (associated with center) were nurse shift, nurse rotation, pain coordinator, written protocols for sucrose analgesia, parental presence authorized 24-hours, night head nurse and teaching status). Interactions between each factor and daytime versus nighttime were included in the model.